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INTRAVASCULAR HEMOLYSIS, THROMBOCYTOPENIA AND OTHER HEMATOLOGIC ABNORMALITIES ASSOCIATED WITH SEVERE TOXEMIA OF PREGNANCY*

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THE pathogenesis of toxemia of pregnancy is not understood. Recently 3 women in whom eclampsia was associated with intravascular hemolysis, thrombocytopenia and clotting defects were studied. These observations, as well as those reported by others, suggest that such an association may not be rare.[1-4] The significance of these observations in relation to the pathogenesis of the symptoms of at least some patients with toxemia of pregnancy is discussed.

Case Report

Case 1. J. K. (U.H. 642-676), a 38-year-old woman (blood Group AB, Rh negative) was admitted to the maternity service on March 18, 1953, when she was 35 weeks pregnant. Her previous pregnancy had been complicated by pre-eclampsia. Before the morning of admission nothing unusual had been observed, except for moderate hypertension during the years since her 1st pregnancy. On that morning she noted for the first time severe epigastric and back pain, headache and scotomas. The urine was very dark.

On admission the blood pressure was 220/140. Fetal heart sounds were present. A generalized convulsion occurred within 25 minutes of admission. Parenteral administration of magnesium sulfate prevented further convulsive episodes. The urine was reddish black and contained large amounts of protein, many granular casts and both hemoglobin and hemosiderin. The plasma at this time was bright red and contained free hemoglobin in a concentration of 184 mg./100 cc. of plasma.

On the following morning there was moderate hemoconcentration, marked thrombocytopenia, prolonged bleeding and clotting times, erythrophagocytosis in vitro, slightly increased erythrocyte osmotic fragility, slight hypoprothrombinemia and delayed clotting of a mixture of plasma and thrombin. The plasma fibrinogen concentration was within the normal range. Petechiae were observed in the area beneath the sphygmomanometer cuff after brief inflation. No abnormal red-cell agglutinins or hemolysins were found in the serum, but both direct and indirect Coombs tests were positive.

An intravenous infusion of ACTH, at a rate of 15 mg. every 8 hours, was started that day about the time that effective labor began in the hope that the platelet concentration would increase and the prolonged bleeding time decrease. The bleeding time just before the start of the ACTH drip was 22 minutes. Within the 9 hours until delivery it had fallen to 7 minutes. Blood loss at parturition was minimal. The stillborn infant was Group A, Rh positive.

Permission for autopsy of the fetus was not obtained. The placenta was normal grossly and histologically.

Treatment with ACTH was continued over the next 26 hours, the total dose being 50 mg. During the last few hours of therapy the blood pressure rose to a maximum of 260/144. The infusion of ACTH was discontinued, and magnesium sulfate was again administered. The bleeding time remained below 10 minutes and the platelet concentration continued to increase (Fig. 1). No new petechiae were evident.

Throughout the remainder of the illness persistent oliguria and poor urinary concentrating power were present, resulting in uremia and marked hyperpotassemia. Hemoglobinemia continued (Fig. 2). On the 7th hospital day the serum potassium concentration reached 8.7 milliequiv. per liter, and there was electrocardiographic evidence of potassium intoxication for the first time. It was decided to use the artificial kidney.

At this time the pulse was of poor volume and grossly irregular. During preparation of the patient for the artificial kidney the heart beat disappeared, and this was followed by cessation of respirations.

Pathological examination was limited to 1 kidney and a segment of liver. Histologically, the liver showed focal periportal necrosis, with evidence of healing. The glomeruli were somewhat ischemic, and the capsules were dilated. Severe hemoglobinuric nephrosis was present (Fig. 4). There was little evidence of regeneration of the tubular epithelium of the kidney.

Case 2. S. H. (U.H. 642-840), a 31-year-old primigravida (Group AB, Rh negative), who was 33 weeks pregnant, was admitted to the maternity service at 12:45 p.m. on March 20, 1953, for severe pre-eclampsia, questionable jaundice and intrauterine death, probably recent.

In November, 1952, when the patient was about 14 weeks pregnant, she noted for the first time gingival bleeding, which originally occurred only occasionally, but later happened nearly every day. Frequent epistaxes started in the following month. Since January she had noticed "bloody spots" on the shoulders. At that time a slight rise in blood pressure to about 140/85 and definite pedal edema were detected. On March 17 she complained of generalized abdominal discomfort and headache. The urine for the first time was dark reddish brown.

At admission on March 20, the blood pressure was 160/90, there was +++ pedal and pretibial edema, and the urine which was dark reddish brown, contained large amounts of protein and many granular casts. The scleras were icteric. Gingival bleeding was present. Many petechiae were seen on the shoulders and abdomen; a large number of new petechiae formed beneath and distal to the sphygmomanometer cuff after brief inflation. No fetal heart beat was heard.

Blood and urine studies revealed hemoglobinemia and hemoglobinuria, a slightly elevated hematocrit, reticulocytosis, slightly increased erythrocyte osmotic fragility, erythrophagocytosis in the buffy coat, negative direct and indirect Coombs tests, thrombocytopenia, prolonged bleeding and clotting times, a somewhat low plasma fibrinogen concentration (182 mg. per 100 cc.), a slightly increased prothrombin time, delayed clotting

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of a mixture of plasma and thrombin, elevated direct and indirect serum bilirubin and choluria.

After prophylactic parenteral administration of magnesium sulfate, an intravenous infusion of ACTH, 15 mg. every 8 hours, was started in an attempt to correct the thrombocytopenia and prolonged bleeding time. Within 16 hours the bleeding time dropped from longer than 22 minutes to 6 minutes.

On the morning after admission the serum sodium and potassium concentrations were 123 and 5.9 milliequiv. per liter respectively, and there was moderate retention of urea. On the following day the patient was comatose. This was attributed to acidosis; the carbon dioxide combining power was 9.5 milliequiv. per liter. The acidosis was successfully treated with sodium lactate and sodium chloride, and she soon regained consciousness. Daily urinary output progressively rose to reach 1000 cc. on the 3d hospital day.

Extensive functional impairment of the liver was indicated by the hyperbilirubinemia, positive cephalin-cholesterol flocculation, elevated serum alkaline phosphatase and low cholesterol esters.

The ACTH infusion was discontinued after 42 hours; the bleeding time remained under 10 minutes, and the platelet count slowly rose.

On the 4th hospital day, the patient appeared much improved. Occasional uterine contractions occurred, but at no time was effective labor established. The blood pressure ranged from 130/70 to 160/90. Suddenly, while she was talking to her family, her speech became slurred, and she rapidly lost consciousness and soon died.

At autopsy pertinent changes were present in the brain, liver and kidneys. There was a recent extensive intracerebral hemorrhage involving most of the right frontal lobe. The source of bleeding could not be found. The liver weighed 950 gm. Grossly, the lobular pattern was intact. Microscopical examination demonstrated diffuse degenerative changes within the parenchymal cells and a subacute inflammation limited primarily to the portal areas. The principal renal lesions were in the glomeruli, which histologically disclosed bright acidophilic foci within the tufts. The acidophilic material was shown to represent thickening of the basement membrane. There were only slight tubular changes. The glomerular and hepatic lesions were believed to be consistent with those found in eclampsia. Grossly and microscopically, the pregnant uterus was normal. The amniotic sac was intact and contained a 1740-gm. fetus. There was no evidence of placental separation. The spleen weighed 85 gm. The follicles were prominent. The bone marrow was hyperplastic and contained numerous megakaryocytes.

CASE 3. E. P. (U.H. 612-396), a 38-year-old multipara, blood Type B, Rh positive, was admitted to the hospital on June 16, 1953, because of severe pre-eclampsia, when she was 37 weeks pregnant. In March moderate hypertension without proteinuria had been noted. The hypertension increased, the blood pressure reaching 190/110 by the day before admission. At that time the urine gave a +++ test for protein, and there was +++ peripheral edema. Episodes of slight gingival bleeding and occasional epistaxes had occurred for at least 2 months before admission. According to the patient similar bleeding had been noted during each of her previous pregnancies, which had otherwise been normal.

On the morning after admission 2 generalized convulsions occurred within 5 minutes. Magnesium sulfate was given both intravenously and intramuscularly, and the convulsions ceased. Urine voided less than 3 hours before the convulsions was pale yellow and contained no benzidine-reacting material. Urine obtained less than ½ hour after the convulsions was pink and, though no erythrocytes were present in the centrifuged sediment, contained free hemoglobin in a concentration of 29 mg. per 100 cc. (Fig. 2). Plasma carefully obtained at this time by means of silicone-coated glassware was bright red and contained 80 mg. of hemoglobin per 100 cc. The plasma fibrinogen level was normal, being 520 mg. per 100 cc.; no agglutinins or hemolysins could be detected in serum obtained shortly after the convulsions.

The tourniquet test was strongly positive; the platelet count was 50,000 (Fig. 1). The clotting time in both plain glass and silicone-coated glass tubes was prolonged. The clotting of a mixture of plasma and thrombin was delayed. Four hours after the convulsions, the plasma was much lighter in color, and the appearance of the urine had changed from bright pink to reddish brown. That afternoon bleeding from the gums was noted. This started and stopped spontaneously twice during the next 18 hours.

Thirty hours after the convulsions apparently normal fraternal twins were delivered by cesarean section without excessive loss of blood. The twins' blood groups were A and B, Rh positive. The mother's platelet count just before delivery was 64,000 (Fig. 1). At birth and 7 days after delivery both twins had normal platelet counts. No agglutination of maternal red cells by plasma from either twin could be demonstrated. The Coombs tests on the twins were negative.

Post-partum bleeding was never excessive. Diuresis promptly followed delivery. The platelet count steadily increased.

TABLE 1. *Studies of the Hemostatic Mechanism in Cases 1, 2 and 3.*

Hospital Day	Clotting Time in Silicone-Coated Tubes			Clotting Time in Glass Tubes			Thrombin Time*			Prothrombin Time		
	case 1 min.	case 2 min.	case 3 min.	case 1 min.	case 2 min.	case 3 min.	case 1	case 2	case 3	case 1 sec.	case 2 sec.	case 3 sec.
0	—	160	—	—	39	—	—	220	—	—	21 (22†)	—
1	630	240	205	39	70	49	52	—	41	19 (15†)	—	24 (22†)
2	300	180	360	34	23	37	48	220	38	17 (16†)	26 (18†)	14 (16†)
3	—	129	265	—	86	75	—	—	40	—	—	15 (16†)
4	—	—	324	—	—	42	—	—	54	—	—	—
5	210	—	—	39	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—	—	17 (18†)
7	—	—	200	—	—	143	—	—	43	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—	17 (16†)
9	—	—	137	—	—	89	—	—	43	—	—	19 (17†)

*Interpolated to normal of 30 sec.

†Figures in parentheses refer to control values.

METHODS

Clotting Time

Clotting times were determined in glass and in silicone-coated tubes; 1 cc. of blood was transferred immediately to each of 3 dry Pyrex test tubes (internal diameter, 11 mm.) and each of 3 silicone-coated tubes of the same diameter. The tubes were stoppered and incubated at 25°C. The first of the plain-glass tubes, starting five minutes after the blood was drawn, was examined for evidence of clotting by tilting of the tubes approximately once a minute. When the blood in the first tube had clotted, the second tube was examined in the same manner, and, in turn, the third. In Tables 1-4 only the clotting time of the third tube has been recorded. In 70 normal persons the clotting time in plain-glass tubes varied from 15 to 52 minutes at

25°C. The average clotting time was 29 minutes, and the standard deviation was ± 9 minutes.

The first of the silicone-coated tubes was tilted after 15 minutes and every 10 minutes thereafter. The second and third tubes were examined at 10-minute intervals after the preceding tube had clotted. In 34 normal persons the clotting time in silicone-lined tubes varied from 66 to 130 minutes; the mean clotting time was 96 minutes, with a standard deviation of ± 18 minutes.

Plasma Fibrinogen

The fibrinogen content of plasma was measured by the method of Ratnoff and Menzie.[5] In 14 normal pregnant women at term the concentration of fibrinogen varied from 275 to 546 mg. per 100 cc. of plasma, the mean being 436 mg. and the standard deviation ± 78 mg. per 100 cc.

Plasma Prothrombin Content, Lysis and Recalcified Clotting Time

The prothrombin content of plasma was determined by a one-stage method in which equal volume of oxalated plasma, rabbit-brain thromboplastin (Cappell), and 0.025 molar solution of calcium chloride were mixed at 37°C. in Pyrex tubes (internal diameter, 8 mm.). Clot lysis time was determined by a method previously described.[6] Recalcified clotting time was performed by mixture of 0.2 cc. of the oxalated plasma with an equal volume of 0.025 molar solution of calcium chloride in Pyrex tubes (internal diameter, 8 mm.). The clotting time was then measured at 37°C.

Plasma Thrombin Time

The thrombin time was measured at 37°C. in mixtures of 0.2 cc. of oxalated plasma and 0.2 cc. of commercial bovine thrombin* in Pyrex tubes (internal diameter, 8 mm.). In each test the clotting time was measured with several concentrations of thrombin, and compared with a normal control. The values in Table 2 have been interpolated to express the clotting time of the patient's plasma at a concentration of thrombin that would give a clotting time of 30 seconds in the control.

Platelets, Osmotic Fragility and Plasma and Urine Hemoglobin

Platelet counts were done with the use of a modification of the solution originally described by Rees and Ecker.[7] Osmotic fragility was determined by the quantitative method of Shen et al.[8] Plasma and urine hemoglobin concentrations were measured by means of a modification of the Bing and Baker methods.[9]

TABLE 1 (*Concluded*).

Hospital Day	Plasma Fibrinogen			Platelet Count			Bleeding Time		
	Case 1 mg./100 cc.	Case 2 mg./100 cc.	Case 3 mg./100 cc.	Case 1 $\times 10^3$	Case 2 $\times 10^3$	Case 3 $\times 10^3$	Case 1 min.	Case 2 min.	Case 3 min.
0	—	182	—	26.5	52.0	—	—	20.0	—
1	360	—	440	50.5	72.0	50.0	22.0	6.0	12.5
2	—	—	—	56.5	—	73.0	3.5	6.5	5.0
3	—	—	—	—	82.5	105.0	2.5	8.0	9.5
4	—	—	—	97.5	98.5	143.0	—	—	—
5	—	—	—	129.0	—	165.0	9.0	—	—
6	—	—	570	127.0	—	—	—	—	3.5
7	—	—	—	—	—	238.0	—	—	—
8	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	298.0	—	—	—

Agglutinins and Hemolysins

The various screening tests used for the identification of auto-agglutinins or iso-agglutinins or hemolysins at various temperatures and pH levels are those described by Ham.[10]

Auto-Antibodies

Direct and indirect Coombs tests, titrations of cold agglutinins, agglutination tests with serum-bovine albumin diluent and agglutination tests with trypsinized normal corpuscles were performed according to the methods of Dacie.[11]

Erythrophagocytes, L. E. Phenomenon, Methemoglobin and Hemosiderin

Erythrophagocytosis was detected using the technic of Zinkham and Diamond.[12] L.E. (lupus-erythematosus) preparations were made according to the method of Weisberger et al.[13] Methemoglobin was determined by the method of Evelyn and Malloy.[14] The ammonium sulfide test was used for the qualitative detection of hemosiderin in the urine.[10]

Results

Studies of the Hemostatic Mechanism (Tables 1 and 2)

In all patients severe thrombocytopenia was present, initial platelet counts being 26,500, 52,500 and 50,000 in Cases 1, 2 and 3 respectively (Fig. 1). Clot retraction was absent or poor. The bleeding time was prolonged. In Cases 1 and 2 it was initially longer than 20 minutes, and in Case 3 it was

*Kindly supplied by Parke, Davis and Company, Detroit, Michigan.

12½ minutes. The tourniquet test was positive in all 3 cases. The bleeding time fell to less than 10 minutes in all patients within 16 hours of the initial studies. The platelet count progressively increased in all, but only in Case 3 did it ever become normal.

Clotting times were measured by methods designed to reveal slight abnormalities. In Case 1

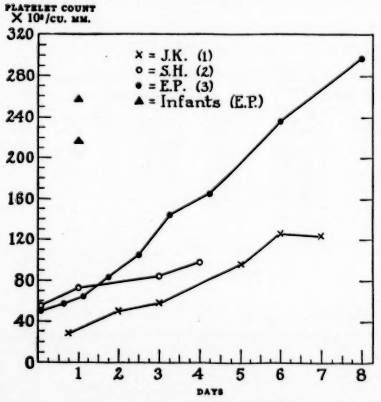

FIGURE 1. *Serial Platelet Counts in Cases 1, 2 and 3 and in the Twin Infants Delivered in Case 3 at the Time of Birth.*

the clotting times in glass tubes were repeatedly normal. In silicone-coated tubes, however, the clotting time when first studied was between 10½ and 19½ hours; subsequently, the clotting time by this method decreased, though not to normal. It was 210 minutes two days before the patient died.

glass was 49 minutes, an equivocally prolonged value, and 205 minutes in silicone-lined tubes. Thereafter, the clotting time in glass was intermittently prolonged, and that in silicone-coated tubes was repeatedly prolonged for days.

TABLE 2. *Clotting Time of Mixtures of 0.1 cc. of Oxalated Plasma and 0.1 cc. of Bovine Thrombin.*

PLASMA	CLOTTING TIME		
	INITIAL THROMBIN CONCENTRATION OF 10 UNITS PER CC. *sec.*	INITIAL THROMBIN CONCENTRATION OF 5 UNITS PER CC. *sec.*	INITIAL THROMBIN CONCENTRATION OF 2.5 UNITS PER CC. *sec.*
Case 1:			
Control (fresh plasma)	8	13	20
Patient (fresh plasma)	12	22	37
Patient's plasma diluted with 3 parts of fresh barium plasma	—	16	26
Patient's plasma diluted with 3 parts of stored barium plasma*	—	24	35
Case 2:			
Control (fresh plasma)	10	22	63
Patient (fresh plasma)	29	64	—
Control (stored plasma)†	31	—	—
Patient's plasma diluted with 1 part of fresh control plasma	13	—	—
Patient's plasma diluted with 1 part of stored control plasma	26	—	—

*Oxalated barium sulfate adsorbed normal plasma stored at −20°C. for several wk.

†Oxalated normal plasma stored at 4°C. for 5 mo.

Studies were performed in each patient to determine whether other defects of the hemostatic mechanism were present. When dilute solutions of bovine thrombin were mixed with each patient's oxalated plasma, the clotting time was prolonged compared with that of a normal plasma. This defect could be corrected partially in Case 1 by the addition of fresh normal plasma treated with barium sulfate but not by such plasma stored at −20°C.

TABLE 3. *Studies of the Hemolytic Episode.*

HOSPITAL DAY	PLASMA HEMOGLOBIN			URINE HEMOGLOBIN			RETICULOCYTES			NUCLEATED RED CELLS			ERYTHROCYTOSIS IN BUFFY COAT		
	CASE 1 *mg./100 cc.*	CASE 2 *mg./100 cc.*	CASE 3 *mg./100 cc.*	CASE 1 *mg./100 cc.*	CASE 2 *mg./100 cc.*	CASE 3 *mg./100 cc.*	CASE 1 %	CASE 2 %	CASE 3 %	CASE 1 *per 100 white cells*	CASE 2 *per 100 white cells*	CASE 3 *per 100 white cells*	CASE 1	CASE 2	CASE 3
0	184	55	80	++	—	29	—	8.2	1.4	0	14.5	0	—	+	0
1	54	43	4	—	—	0	0.6	10.4	4.6	0	—	0	++	—	0
2	21	—	—	—	—	—	3.7	9.7	6.4	—	11	—	—	—	0
3	—	—	—	—	—	—	—	—	5.9	—	—	—	—	—	—
4	—	—	—	—	—	—	6.8	11.7	—	—	—	—	—	0	—
5	—	—	—	—	—	—	6.1	—	7.2	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	7.2	—	—	—	0	—	—
7	—	—	—	—	—	—	8.2	—	—	—	—	—	—	—	—
10	—	—	—	—	—	—	—	—	6.4	—	—	0	—	—	—

In Case 2 the clotting time in glass varied considerably at different times, both normal values and values as long as 86 minutes being noted. The clotting time in silicone-coated tubes was moderately prolonged, being 160 minutes when first determined; on the day before death a normal clotting time was obtained. In Case 3 the initial clotting time in for several weeks. In Case 2 the effect of oxalated normal plasma not treated with barium sulfate was tested (Table 2); fresh plasma shortened the clotting time on the addition of thrombin, but plasma that had been stored at 4°C. for five months was ineffective. Similar data were obtained in Case 3. These observations suggest that in each patient the ab-

normally long clotting times of mixtures of plasma and thrombin were due to a deficiency in some factor present in fresh normal plasma.

The alterations in the thrombin clotting time made estimations of the prothrombin time unreliable. In Case 1 the prothrombin time was 19 seconds, compared with a control of 15 seconds. Dilution of plasma with normal plasma treated with barium sulfate suggested that the prothrombin activity of this patient's plasma was 50 per cent of that of the control plasma. The prothrombin time in Case 2 on initial study was normal. Two days later, when other tests indicated the presence of severe hepatic damage, the prothrombin time was 26 seconds (control of 16 seconds). In Case 3 the prothrombin time was normal.

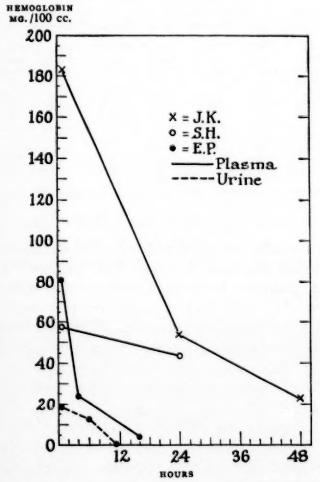

FIGURE 2. *Rates of Disappearance of Hemoglobin from the Plasma in Cases 1, 2 and 3 and from the Urine in Case 3.*

The clotting time of oxalated plasma on recalcification was normal in each case. Each patient's plasma corrected the defect in hemophilic plasma. Abnormally rapid fibrinolysis was observed before delivery in Case 1, a recalcified clot lysing within 24 hours. The clot lysis times were normal in Cases 2 and 3, being 3 and 4 days, respectively.

Studies of the Hemolytic Episode (Fig. 1 and 2 and Table 3).

Hemoglobinuria was observed in all 3 cases. In Case 1 it was first demonstrated 45 minutes after the eclamptic convulsion and persisted for at least 3 days. In Case 2 the plasma hemoglobin concentration shortly after admission was 55 mg. per 100 cc. and remained elevated for at least 24 hours. In Case 3 the plasma hemoglobin concentration 15 minutes after the convulsions was 80 mg. per 100 cc.; it returned to normal within the next 28 hours. Urine voided by the patient less than 3 hours before the convulsions was free of hemoglobin. Hemoglobinuria in a concentration of 29 mg. per 100 cc. was found in the specimen obtained less than half an hour after the convulsions. The urine was free of hemoglobin within 11 hours. Hemosiderin was identified in the urine of all patients early but was absent from all within 4 days. Methemoglobin was never demonstrated in abnormal concentrations.

The indirect serum bilirubin was elevated in all cases. In Cases 1 and 3 it had returned to normal by the sixth and first days respectively. In Case 2 both the direct and indirect serum bilirubin remained elevated until the time of death. Cases 2 and 3 showed markedly elevated urine urobilinogen excretion; studies were not done in Case 1.

Each patient showed a marked reticulocytosis. Associated with the reticulocytoses was a progressive fall in the hematocrit in all patients. Nucleated red blood cells were present in stained films of peripheral blood in Cases 1 and 2; none were seen in Case 3. Similarly, erythrophagocytosis was seen in the buffy coat in Cases 1 and 2 but not in Case 3. Erythrophagocytic indexes were low, however, being 2.2 and 0.2 per cent in Cases 1 and 2, respectively.

TABLE 3 (*Concluded*).

Hospital Day	Increased Osmotic Fragility			Direct Coombs Test			Urine Hemosiderin			Urine Urobilinogen			Hematocrit		
	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1 *Ehrlich units/2 hr.*	Case 2 *Ehrlich units/2 hr.*	Case 3 *Ehrlich units/2 hr.*	Case 1 %	Case 2 %	Case 3 %
0	—	+	0	—	0	0	—	++	++	—	—	—	—	47	38
1	+	—	0	++	—	0	++	+	—	—	—	1.0	47	43	35
2	—	+	0	+	0	0	—	—	—	—	6.9	1.4	38	41	35
3	—	—	—	—	—	—	0	0	0	—	—	6.4	35	38	34
4	—	—	—	—	0	—	—	—	—	—	—	—	—	31	33
5	—	—	—	—	—	—	—	—	—	—	—	—	30	—	32
6	—	—	—	0	—	—	—	—	—	—	—	—	—	—	—
7	—	—	—	—	—	—	—	—	—	—	—	—	31	—	32
10	—	—	—	—	—	—	—	—	—	—	—	2.1	—	—	30

Cases 1 and 2 each showed a slightly increased erythrocyte osmotic fragility. Hemolysis began at a saline concentration of 0.60 per cent; however, the 50 per cent and 75 per cent hemolysis points were within normal limits. This finding was correlated with the presence of a small number of spherocytes observed in peripheral blood smears. The osmotic fragility was normal in Case 3.

Repeated attempts were made to demonstrate auto-agglutinins or iso-agglutinins or hemolysins in the blood. None were detected by any of the battery of tests used. The Donath–Landsteiner and hemolysis tests with acidified serum were negative in all. Case 1 showed a low-titer (1:16) positive direct Coombs test on admission that became negative during the next 4 days. This patient's serum gave a positive indirect Coombs test with Rh-positive (D) cells but a negative test with Rh-negative (CDE-negative) cells. In Cases 2 and 3 the direct and indirect Coombs tests were repeatedly negative. Cold agglutinin titers were not elevated. None of the patients' serums agglutinated trypsinized normal red cells.

TABLE 4. *Studies of Hepatic and Renal Function.*

Hospital Day	Cephalin-Cholesterol Flocculation			Cholesterol Esters			Alkaline Phosphatase			Direct Serum Bilirubin			Total Serum Bilirubin		
	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3
				%	%	%	*Shinowara units*	*Shinowara units*	*Shinowara units*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	0	—	—	90.0	—	—	7.9	0.9	7.6	0.8	2.8	11.0	2.2
2	—	—	—	—	—	—	—	—	—	1.5	7.1	0.3	1.8	14.0	1.2
3	—	—	—	—	29.0	—	—	29.2	—	—	8.4	—	—	12.0	—
4	—	+++	—	—	—	—	—	—	—	—	8.1	—	—	13.0	—
5	+++	—	—	—	—	—	7.8	—	—	—	—	0.4	—	—	1.1
6	—	—	—	60.0	—	—	—	—	—	0.3	—	—	1.2	—	—
7	—	—	0	—	—	—	—	—	—	0.4	—	0.3	0.7	—	1.1
13	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Erythrocytes from each twin delivered in Case 3 showed no auto-agglutination in albumin and were Coombs negative. The plasma from these infants did not agglutinate maternal washed red cells in either a saline or an albumin medium.

L.E. preparations were done in all cases. Rosettes but no typical L.E. cells were seen in Case 1. Neither rosettes nor L.E. cells were observed in Cases 2 and 3.

FIGURE 3. *Section of the Liver in Case 1, Showing Discrete Periportal Necrosis.*

Evidence of Hepatic Dysfunction (Table 4)

Severe liver impairment was demonstrated only in Case 2. A progressively increasing hyperbilirubinemia occurred. The urine persistently contained bile. The total serum cholesterol was 163 mg. per 100 cc., but less than 30 per cent was esterified. The serum alkaline phosphatase was 29.2 Shinowara units. Cephalin-cholesterol flocculation was +++, but the thymol turbidity was normal.

In Case 1 only transiently abnormal liver-function tests were noted, and in Case 3 no evidence of functional impairment of the liver was detected.

Histologic changes were not similar in the livers in Case 1 and 2. The liver in the former (Fig. 3) showed focal periportal necrosis with relatively normal parenchyma elsewhere, whereas in Case 2 there was diffuse parenchymal cellular degeneration, with no distinct foci of necrosis (Fig. 4).

Apparent Nature of Renal Abnormalities

Initially, similar changes in renal function were observed in all patients, as evidenced by proteinuria, cylindruria, lack of normal concentrating and diluting powers and azotemia (Table 4). In Case 1 the

oliguria persisted, with progressive azotemia and hyperkalemia. On the day of death the blood urea nitrogen had reached 156 mg. per 100 cc.; the serum potassium was 8.7 milliequiv. per liter. In Case 2 the oliguria was less marked, the twenty-four-hour urinary output rising to 1000 cc. 3 days after admission. The concentrating power was poor, however, and the blood urea nitrogen at the time of death, 4 days after admission, was 79 mg. per 100 cc.

Case 3 showed initial transient oliguria followed by diuresis, the twenty-four-hour urine output reaching a maximum of 3000 cc. 5 days after admission and 3 days after termination of the pregnancy. At this time the blood urea nitrogen was 44 mg. per 100 cc.

The histologic alterations in the kidneys in Cases 1 and 2 differed. In the former (Fig. 5) the predominant lesion was marked hemoglobinuric nephrosis, with little change in the glomeruli. In the latter (Fig. 6) the kidney contained many acidophilic

TABLE 4 (*Concluded*).

Hospital Day	Test for Bile in Urine			Urinary Output			Blood Urea Nitrogen			Serum Potassium			Serum Sodium		
	Case 1	Case 2	Case 3	Case 1 cc.	Case 2 cc.	Case 3 cc.	Case 1 mg./100 cc.	Case 2 mg./100 cc.	Case 3 mg./100 cc.	Case 1 milli-equiv./liter	Case 2 milli-equiv./liter	Case 3 milli-equiv./liter	Case 1 milli-equiv./liter	Case 2 milli-equiv./liter	Case 3 milli-equiv./liter
0	—	—	—	—	300+	525	—	—	—	—	—	—	—	—	—
1	0	++	0	340	650	1020	32	63	17	5.2	5.9	—	140	123	132
2	—	++	—	325	900	3200	—	—	27	—	—	3.7	—	124	126
3	—	+++	—	660	1000	3800	79	75	33	5.9	5.0	5.0	123	120	127
4	—	—	—	300	—	3400	—	79	35	—	5.2	3.8	—	138	133
5	—	—	—	270	—	—	128	—	44	6.3	—	—	116	—	—
6	—	—	—	200	—	—	142	—	24	6.4	—	5.0	133	—	145
7	—	—	—	—	—	—	156	—	30	8.7	—	—	135	—	—
13	—	—	—	—	—	—	—	—	14	—	—	—	—	—	—

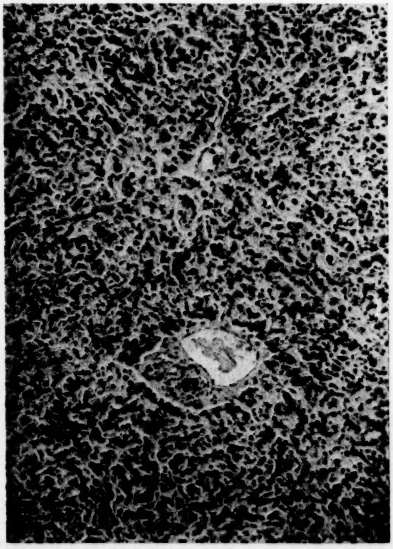

FIGURE 4. *Section of the Liver in Case 2, Showing the Diffuse Nature of the Degenerative Parenchymal Changes.*

FIGURE 5. *Renal Tubules in Case 1, Showing Severe Epithelial Damage.*

Numerous pigmented casts are present. The glomerular changes are slight.

foci within the glomerular tufts, presumably because of focal thickening of the basement membrane. Considerable amounts of protein were deposited in many of the tubules; otherwise, the tubular changes were slight.

Discussion

Hypertension, proteinuria and edema in the last trimester of pregnancy were present in each case.

Each patient had an acute hemolytic episode that, as far as could be determined, was not a manifestation of the usual hereditary hemolytic anemias, and, therefore, must be assumed to have been of the so-called "acquired" type unassociated with demonstrable abnormal antibodies except a slightly positive Coombs test in Case 1.

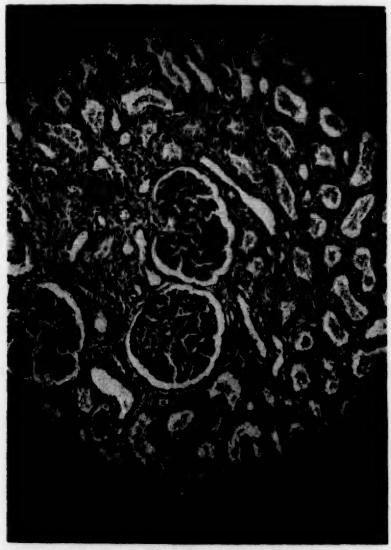

Figure 6. *Glomerular Tufts in Case 2, Showing Numerous Acidophilic Foci.*
The tubular epithelium is little altered.

The pathogenesis of the defects in clotting in these patients was probably complex. In each, the clotting time, measured in silicone-coated tubes, was prolonged. Each of these patients had thrombocytopenia, an abnormality that prolongs the clotting time in silicone-coated tubes.

In all, moreover, the clotting time of a mixture of plasma and thrombin was prolonged compared with normal plasma. This defect appeared to be the result of a deficiency of a factor present in fresh normal plasma. A similar prolongation of the thrombin time may be present in the plasma of patients with cirrhosis of the liver or multiple myeloma, but this test is negative in uncomplicated thrombocytopenia.[15]

Any attempt to explain the association of hemolysis, thrombocytopenia and clotting defects with what appears to have been pre-eclampsia or eclampsia raises the following questions: Are the observed hematologic changes causally related to severe toxemia of pregnancy? If this is so, are they a result of the alterations commonly ascribed to toxemia of pregnancy? Are the hematologic events due to some other disease that occurred coincidentally with toxemia in the 3 patients?

Of diseases besides pre-eclampsia or eclampsia that may have been present in these cases, at least thrombotic thrombocytopenic purpura and lupus erythematosus deserve consideration. It is believed that thrombotic thrombocytopenic purpura is excluded by the absence of vascular lesions resembling in any way those described in this disease by Orbison.[16] The variability found both clinically and morphologically in lupus erythematosus makes the task of identifying or excluding this disease difficult. Hematologic changes, vascular lesions and central-nervous-system abnormalities have often been described. Likewise, the histologic changes seen in the liver and kidneys in Cases 1 and 2 are not inconsistent with lupus. Repeated attempts were made to demonstrate L.E. cells in the peripheral blood of these patients. In Case 1, on the day after admission, rosettes were seen. Otherwise, all preparations were negative. The failure to find L.E. cells does not exclude the presence of lupus.

However, certain observations in these cases and in a few other pregnant patients studied at University Hospitals of Cleveland, as well as the findings of other investigators, suggest that the hematologic changes are directly related to toxemia of pregnancy. Two and a half years ago hypertension, edema, proteinuria and convulsions occurred in a patient nearing term in her sixth pregnancy (U.H. 601-554). Associated with these findings were transient hemoglobinemia, hemoglobinuria, an elevated indirect serum bilirubin, nucleated red blood cells in the peripheral blood, progressive anemia, azotemia, oliguria and positive cephalin-cholesterol flocculation. Neither platelet counts nor the more subtle tests for clotting defects described above were done. The patient's recovery has been judged complete. No evidence of lupus erythematosus has appeared in the subsequent two and a half years since her illness.

Two other cases seen more recently also suggest that these hematologic abnormalities may be intimately concerned with toxemia of pregnancy. D.W. (U.H. 623-183), a sixteen-year-old Negress who was thirty-seven weeks pregnant, was ad-

mitted to the hospital for nausea and vomiting. Neither hypertension nor proteinuria was present at that time. There were, however, unusual hematologic changes. A slightly elevated serum indirect bilirubin, moderate reticulocytosis, nucleated red blood cells in the peripheral blood and an elevated urine urobilinogen were found. No cause for the transient hemolytic process could be determined. Within the next two weeks the blood pressure reached 150 systolic, 100 diastolic, and significant proteinuria was detected. Spontaneous labor and delivery occurred at this time. Thrombocytopenia was not found but a definitely delayed clotting of a mixture of plasma and thrombin was observed. After delivery the blood pressure soon returned to normal, and the proteinuria became progressively less.

B.Y. (U.H. 647–189), a twenty-six-year-old woman, pregnant for the first time, while in the tenth lunar month of pregnancy manifested hypertension, edema, proteinuria, headache and epigastric pain. Shortly after admission studies revealed moderate reticulocytosis, a prolonged clotting time in silicone-coated tubes, a prolonged bleeding time and a positive tourniquet test. The platelet count and thrombin time were normal. No evidence of a hemolytic episode other than the reticulocytosis was elicited. The clotting times were repeatedly abnormal.

Kistner and Assali[3] described a case of acute intravascular hemolysis and lower-nephron nephrosis complicating eclampsia. Their data indicate that transient thrombocytopenia was also present. No mention was made of any studies of the clotting mechanism in this patient. Dr. Leon Chesley, in a personal communication, states that in 3 of the last 4 fatal cases of eclampsia observed by him at the Margaret Hague Hospital hemoglobinemia and hemoglobinuria were observed.

Schneider,[1] while doing serial plasma fibrinogen studies in cases of eclampsia, noted transient gross hemoglobinemia in 4 out of 5 cases. In all, the plasma was grossly free of hemoglobin by the day after the convulsive episode. No mention was made of any studies of platelets or of the blood-clotting mechanism other than fibrinogen concentrations in these patients.

The presence of thrombocytopenia in severe toxemia has previously been detected. Stahnke,[17] in 1922, stated that thrombocytopenia was present in severe cases of toxemia of pregnancy associated with hemolysis. Ward and MacArthur,[18] in 1948, reported that in 7 pre-eclamptic and eclamptic patients blood platelets were definitely lower than normal. Dieckmann[4] estimates from his own experience and from reports of others that the cause of death in 15 to 20 per cent of fatal cases of eclampsia is extensive cerebral hemorrhage. The presence of thrombocytopenia in some cases of eclampsia may help explain this high incidence of fatal cerebral hemorrhage.

The hepatic and renal lesions present in Cases 1 and 2, although differing in each, were consistent with those found by others in eclampsia. Sheehan[19] described both focal periportal lesions and diffuse early necrobiotic changes in the liver. He believes that the latter lesion, as in Case 2, is associated with fatal eclampsia but is not necessarily related to eclamptic convulsions, since it may be found in "eclampsia without fits." The glomerular changes in Case 2 also demonstrate what Sheehan regards as the essential renal lesion of eclampsia, although he differs in his interpretation of the lesion, believing it to represent focal endothelial fibril proliferation rather than thickening of the basement membrane.

ACTH was administered by constant intravenous infusion in Cases 1 and 2 in an attempt to correct the thrombocytopenia and the prolonged bleeding times. Its use was accompanied by a moderate rise in platelet concentration and a decrease in the bleeding time to normal. However, no ACTH was given in Case 3, in which the bleeding time likewise decreased. Its use in Case 1 was accompanied by a progressive rise in blood pressure to a maximum of 260 systolic, 160 diastolic. In Case 2 while ACTH was being given the patient became more drowsy and finally comatose. She was severely acidotic and responded well to intravenous infusion of sodium lactate. A marked augmentation of her initial moderate hypertension was not observed during its administration. Thus, there is no evidence that ACTH was of any value in these patients, and the possibility that its use was detrimental must be considered.

The various screening tests described above for the detection of circulating agglutinins or hemolysins were negative, with the exception of a positive direct Coombs test in Case 1. Attempts to demonstrate in the fetal blood antibodies active against maternal erythrocytes in Case 3 were also unsuccessful. The occurrence of a hemolytic episode of the acquired type with thrombocytopenia, however, suggests the presence of an immunologic process.

The possibility that an immunologic mechanism is involved in the pathogenesis of pre-eclampsia and eclampsia has previously been suggested by other investigators but remains unproved.[20]

Summary

Three cases of eclamptogenic toxemia of pregnancy complicated by hemoglobinemia, hemoglobinuria, thrombocytopenia and clotting defects (prolonged clotting time in silicone-coated tubes and delayed clotting of a mixture of plasma and thrombin) are described. Other cases of toxemia of pregnancy showing at least some of these hematologic changes are more briefly discussed.

The probability that these hematologic abnormalities are associated intimately with at least some cases of pre-eclampsia or eclampsia and that an immunologic process may be involved is considered.

Since the preparation of this paper, 19 other patients with severe pre-eclampsia or eclampsia have been studied. The data from these patients, which extend the observations described above will be reported subsequently.

We are indebted to Dr. J. L. Orbison, who reviewed the pathological material, and the Misses Joan Colopy, Lois Dolhar and Angela Pasquariello, who performed many of the laboratory procedures done on these patients.

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RHABDOMYOSARCOMA OF THE TONGUE*

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PHILADELPHIA

PRIMARY rhabdomyosarcoma of the tongue is a rare condition to which no reference is available for a complete pathological description or a sound therapeutic approach. The physician confronted with a malignant tumor of the tongue that is grossly and histologically unlike carcinoma must refer to a confused and sparse literature to cope with the question of exact diagnosis, treatment and prognosis. We attempted to solve this problem by applying concepts based on our experience and what we could learn in the literature about oral carcinomas, lingual sarcomas generally and rhabdomyosarcoma of the extremities. This paper is a compilation of the material that we considered most worth while and applicable to rhabdomyosarcoma of the tongue.

History

Since 1867, when Durham[1] first described a case of lingual sarcoma, early case reports[2-5] and later reviews[6-9] have appeared. Goldstein,[9] after an extensive study of the literature, found and reviewed 65 cases of lingual sarcoma. Thus, the total number of all types of sarcoma of the tongue appears to be small; rhabdomyosarcoma of the tongue is even rarer. In 1946 Stout[10] collected all the cases he could find in an exhaustive review, the series consisting of 116 cases of rhabdomyosarcoma in various sites throughout the body, only 10 of which involved the tongue. Since the publication of this article, a number of cases of rhabdomyosarcoma found in other somatic sites have appeared in the literature, but to our knowledge only 1 other case[11] in which this tumor arose in the tongue has been reported. During a twenty-year period, 1929-1949, at Memorial Cancer Center in New York City there were 717 soft-tissue sarcomas, of which 100 were rhabdomyosarcoma[12]; not one involved the tongue.

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Pathological Picture and Classifications

Tumors of the tongue not only arise from muscle-cell origin but also may arise from nerve structures, blood vessels, lymphatic system or fibrous and fatty tissues within the muscle bundles.[13] The position of rhabdomyosarcoma in the whole group of lingual mesoblastic tumors is demonstrated in Table 1.

The development of the normal muscle cell gives a key to the complicated problem of classifying the

tumor of muscle origin (Table 2). The myoblast or primitive round cell develops into the spindle cell, which differentiates into the multinucleate stage of the syncytial muscle fiber; myofibrils arise within this cell, producing first longitudinal and then cross striations. Theoretically, then, a tumor may arise at any one stage in the development of the cell, or it may arise at the transitional phases. Furthermore, the tumor may be composed of two or more stages of cellular differentiation.

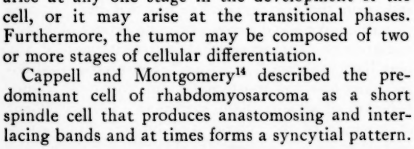
TABLE 1. *Nonepithelial Tumors of the Tongue.**

TISSUE-CELL TYPE	TUMOR
Fibrocyte	Fibroma, fibrosarcoma
Lymphoid tissue	Lingual tonsil, lymphosarcoma, lymphoepithelioma
Blood vessel	Hemangioma, hemangiosarcoma
Lymphatics	Lymphangioma
Nerve	Neurofibroma, neurilemmoma, neurogenic sarcoma
Fat	Lipoma, liposarcoma
Muscle (striated)	Myoblastoma (?), rhabdomyoma, rhabdomyosarcoma

*Primitive cell precursor – mesoblast.

Cappell and Montgomery[14] described the predominant cell of rhabdomyosarcoma as a short spindle cell that produces anastomosing and interlacing bands and at times forms a syncytial pattern.

TABLE 2. *Development of the Muscle Cell and Various Tumors Derived From It.*


Myoblast
monuclear spindle cell
multinuclear syncytial cell
adult striated muscle cell
?
myoblastoma (benign)
poorly differentiated rhabdomyosarcoma (Grade 3 and 4), most malignant
rhabdomyoma (benign); rhabdomyosarcoma well differentiated (Grade 1 and 2), highly malignant.

Cross striations were found with difficulty. These cells were associated with giant cells and with round cells of several types. Stout[10] described a raquet-shaped cell with a single nucleus at the rounded end, and a strap-shaped cell with two or three nuclei arranged in tandem. With special stains such as Masson's trichrome, Heidenhain's hematoxylin and phosphotungstic acid and hematoxylin stain, cross striations, longitudinal myofibrils or some vague suggestion of their formation should be distinguishable in most cases.

Distinction between rhabdomyosarcoma and myoblastoma in the literature is not always clearly made. In fact, myoblastoma was not described in the literature until 1926, when Abrikossoff[15] presented 5 cases, 3 of which arose in the tongue. These tumors are composed of large cells with small pyknotic nuclei and are characterized by large amounts of coarsely granular cytoplasm, much of which is eosinophilic. The cells are described as resembling myoblasts or spindle-shaped cells. They are not highly pleomorphic; there is little active mitosis, and despite the absence of striations they are not very primitive. Earlier, Klinge[16] and recently other authors[17-19] maintained that myoblastomas were degenerative or regenerative lesions of the muscle fibers; Leroux and Delarue[20] believed that they represented merely a local accumulation of histiocytes as a manifestation of a general metabolic process. Ashburn and Rodger[21] regarded myoblasts as originating from the Schwann cell or altered fibroblasts of neural origin. Ewing,[13] Murphy, Dockerty and Broders[22] and Crane and Tremblay[23] stated that the myoblastomas were rare; they believed that the great majority of these tumors were slow growing or even stationary, most being well encapsulated and benign.

Abrikossoff[15, 24] distinguished four varieties of striated muscle tumors: those made up of myoblasts without striations; similar tumors showing infrequent longitudinal or cross striations that are imperfectly developed; tumors with giant cells of the syncytial type, frequently multinuclear, with or without striations; and atypical myoblastic sarcoma with longitudinal and cross striations and pleomorphic cells — that is, in some areas sarcomatous and in others showing more highly differentiated cells. Cappell and Montgomery[14] later simplified this into two groups: tumors showing well defined cross striations ("malignant rhabdomyoma sarcomatodes") and those lacking them ("myoblastomas").

A pleomorphic type of tumor may grade almost imperceptibly from myoblastoma to the rhabdomyosarcoma, since there is no absolute line of demarcation between the two.[14] Ewing[13] found it possible to trace all stages at the gradual transformation of round undifferentiated cells into elongated branching cells and finally into large cells with fibrils. It is this, according to Murphy et al.,[22] that has caused the greatest confusion in the literature.

In differentiating these tumors Howe and Warren[25] classified as rhabdomyosarcoma or rhabdomyoma any tumor of this type that had "an appreciable number" of cells with cross striations. Cappell and Montgomery[14] included cases showing "any" cross striations in this category. In questionable cases, Willis[17] believed that where anaplasia deprived the cells of a rhabdomyosarcoma of the distinctive character of striated muscle cells, especially cross striations, positive histologic recognition of the true nature of the tumor became impossible.

Menetrier and Surmont,[26] Loubat and Petit,[27] Stobbe and Dargeon[28] and Kudlich[8] described sarcomatous growths arising during early infancy. In his review Coughlin[7] included 3 congenital tumors of the tongue and 4 additional cases occurring in the postnatal and infancy periods (seven weeks, ten months, two years and four years). Ross,[29] on the other hand, rejected these so-called congenital

sarcomas occurring during the first year, since he believed that they exhibited an angiomatous element. Ewing[13] contrasted an adult type of rhabdomyosarcoma arising from mature muscle tissues and an immature type found especially in infants and children, some of which may arise from embryonal cells or embryogenic disturbances. The classification of these tumors into mature and immature types adequately covers the distinction.[13]

Spencer and Cade[30] seriously questioned the so-called round-cell sarcoma. Even among those recorded under that term, a minority failed to supply sufficient proof that they were malignant connective-tissue tumors. Greater obscurity still hangs over the case in which sarcoma apparently combines with carcinoma. Regarding the small round-cell sarcoma, Ewing[13] emphatically stated that with rare exceptions such round-cell growths are lymphosarcoma, endothelioma or small-cell carcinoma. Much of the same uncertainty surrounds the origin of the so-called large round-cell sarcoma.[13]

Clinical Picture

Coughlin's[7] review of 53 patients with lingual sarcoma in which the age was known described 3 patients who had the tumor at birth. The ages of the others varied from seven weeks to seventy-one years, with a peak of 27.4 per cent in the fourth decade. Four patients were four years of age or under. Stout,[10] reviewing 116 cases of rhabdomyosarcoma found throughout the body, observed that the ages ranged from birth to eighty-four years, with an average of forty-two and one-tenth years and a preponderance of cases in the fifth and sixth decades.

The insidious onset of a painless mass is the usual, expected picture in this disease. Stout,[10] in his review of patients with rhabdomyosarcoma, found that 88.5 per cent had swelling as their only symptom. In his cases pain or trauma was unusual. The tumor may interfere with speech, if it lies in the anterior two thirds of the tongue, or with deglutition if located in the posterior third. Coughlin[7] reported lingual sarcoma slightly more common on the right side of the tongue and toward the base. The masses of his series varied in size from that of a pea to one weighing 400 gm., the mass was usually intraglossal and bulging toward the dorsum. It was described as rounded, firm or soft, depending on the amount of collagen present, elastic and white or pink on cut section. Coughlin,[7] in contrast to most authors, noted ulceration to be fairly common, occurring in 11 out of 29 cases (in his series of 60) in which the presence or absence of ulceration was noted. Ulceration was more prevalent where the tumor mass pressed against the teeth. Barrett and Miller[31] mentioned hypersalivation, fetor oris and rarely hemorrhage as being present in the late stages.

Metastases to lymph nodes were found in 15 out of 37 cases, or 40 per cent, according to Coughlin, who thought that blood-vessel dissemination was more frequent than lymphatic spread. Willis[32] stated that rhabdomyosarcoma (all sites) yielded lymph-node metastases in a high proportion of cases and that these might be extensive. Of the 66 cases of rhabdomyosarcoma of various parts of the body that recurred, 38, or 61 per cent, were metastases, according to Stout.[10] Metastases appeared in the lungs in 23, in the lymph nodes in 10, in the skin and subcutaneous tissues in 8, in the pleura in 7, in the bones in 5, in the liver in 3, in the kidney, adrenal glands and mediastinum in 2 each and in the pancreas, ovary and brain in 1 each. There were generalized metastases in only 5 cases.

Treatment and Prognosis

Although reports in the literature are equivocal, radiation therapy, generally, has not been proved of value. We have found only one report of heavy radiation in a case of rhabdomyosarcoma of the maxillary antrum.[33] Jönsson[34] considered rhabdomyosarcomas the most malignant and most radioresistant of all soft-tissue sarcomas. The treatment of sarcoma of the tongue and lingual rhabdomyosarcoma is early radical excision.[35] Of the two the results with sarcoma have been better. The prognosis of lingual rhabdomyosarcoma is unfavorable, and the course, according to Ewing,[13] is usually rapidly progressive. Fripp and Swan[36] followed 24 cases of lingual sarcoma by letters to the surgeons who had reported them and found 11 patients to be alive and well six months to thirteen years after operation. Of 46 operations for lingual sarcoma reported by Coughlin,[7] 10 patients were without clinical recurrence two years or more after operation. Recently, Holton[37] presented a case of round-cell sarcoma of the tongue in which the patient was alive and well thirty-two years and ten months after operation. Barrett and Miller[31] described a case of primary sarcoma of the tongue radically removed, with death from recurrence. Ross[29] also reported a lingual sarcoma treated with hemiglossectomy, a block dissection of the glands on one side of the neck and x-ray therapy. The patient was well and free from recurrence one and a half years after the operation.

Primary lesions of the tongue were found in only 10 cases by Stout[10] in his review of 116 cases of rhabdomyosarcoma in various sites throughout the body. All 10 patients had excision of the tumor mass. Four of them died of recurrences thirteen months to four and a half years after operation, and 1 was known to have a recurrence; the 5 remaining patients were not followed. In all the 116 cases there were 108 patients in whom operative treatment was attempted. Eighty had a simple local excision. Five of these were without recurrence less than five years later, only 2 were without re-

currences more than five years after operation, and the rest either were not followed or had recurrences; 16 patients had primary amputation after biopsy. Two cases were considered operative deaths; 6 patients had recurrences or metastases, and only 1 patient was alive and well eleven years after the operation. The remaining 7 patients were not followed. Thus, only 3 patients in the entire series were known to be living and well after five years, and none of these cases were of lingual origin.

Since Stout's article, there have been many reports in the literature concerning rhabdomyosarcoma in various sites throughout the body. We know of only one article, by Wood and Williams,[11] describing the tongue as the primary site of the tumor; this was found in a three-month-old Mexican girl with a history of a mass in the posterior aspect of the tongue since birth. After attempted removal, the child died in the immediate postoperative period.

Case Report

H. A. (No. 32893), a 47-year-old truck driver, first seen on October 30, 1949, gave a history of having a mass on the left side of the tongue for 9 weeks. The tumor had started as a small ulcer and was construed as a "gum boil." It grew rapidly until it interfered with mastication, but was not painful and did not bleed. There was no difficulty in swallowing. The past history, family history and system review were noncontributory.

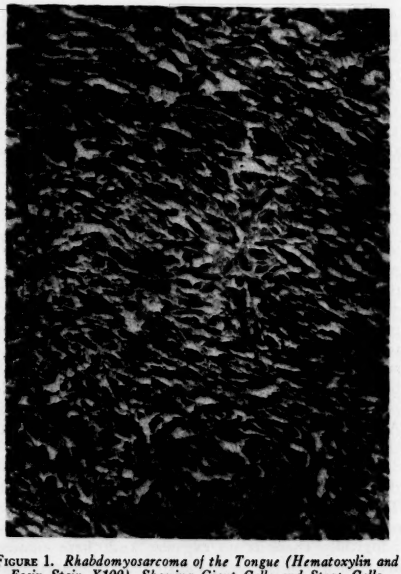


Figure 1. *Rhabdomyosarcoma of the Tongue (Hematoxylin and Eosin Stain X100), Showing Giant Cells and Strap Cells. Even at low power, mitotic phases are discernible.*

Physical examination revealed a firm, irregularly rounded, pedunculated mass approximately 3 by 2 by 2 cm. on the left lateral aspect of the tongue, 3.5 cm. from the tip. This lesion was opposite the mandibular 2d molar which was a loose, discolored tooth with a sharp snag. Of the 14 teeth present, at least 6 were carious and loose. There was no cervical lymphadenopathy. The remainder of the examination was within normal limits.

Under local anesthesia a biopsy was performed, the visible tumor mass being removed; the patient was advised to have extraction of the remaining teeth and hygienic preparation of the mouth.

The biopsy was reported as showing ulceration and obliteration of the surface epithelium by an extremely anaplastic, actively growing neoplasm made up of large spindle cells containing large vesicular nuclei. In many areas there were large plasmodial giant cells containing many small nuclei and a large, folded-over nucleus. In many of the cells myofibrillae were prominent. The deeper portions of the tumor were widely infiltrated, and mitotic figures were frequent (Fig. 1). A pathological diagnosis of rhabdomyosarcoma of the tongue was made (Fig. 2).

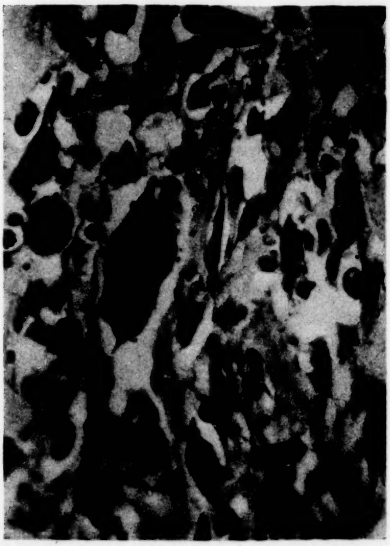


Figure 2. *Rhabdomyosarcoma of the Tongue (Hematoxylin and Eosin Stain X430).*

The patient was admitted to the hospital on November 4, 1949. Routine laboratory work was found to be within normal limits. An x-ray film of the chest was reported as normal, and neurologic examination was negative.

A radical en bloc resection of the left half of the tongue and the left side of the neck was performed in continuity. Preliminary tracheotomy was first carried out, 1 week before operation, a No. 6 tracheotomy tube being used. Through this, endotracheal anesthesia was administered for the radical resection.

Skin flaps were created by means of a T-shaped incision in which the horizontal arm extended from the mastoid process across the neck at the level of the hyoid bone to a point opposite the genoid process of the mandible, and the vertical limb extended from the angle of the mandible to the clavicle. Skin flaps were developed to include the platysma (for better circulation), and the entire neck was bared down to the envelop-

ing layer of the cervical fascia from the midline to the trapezius muscles and from the lower margin of the mandible to the clavicle.

Dissection of the supraclavicular and posterior cervical triangles was begun from below and posteriorly and continued upward to include the insertion of the sternomastoid muscle, the internal jugular vein at the lowermost aspect of the wound, together with the carotid sheath, external carotid artery, the omohyoid muscle, and all the loose areolar and lymphatic tissue available in the supraclavicular and posterior triangles. The levator scapulae, scaleni, ribbon muscles, brachial plexus and phrenic nerve were bared. Care was taken to preserve the accessory and vagus nerves.

The suprahyoid dissection was then carried out, and all tissues were added to the en bloc dissection, leaving the mylohyoid and anterior belly of the digastric muscle clean. The dissection began posteriorly by freeing the sternomastoid from its origin on the mastoid process; the stylohyoid and posterior belly of the digastric muscles were included in the resection, exposing the jugular vein and the carotid up to the base of the skull. The internal jugular vein was ligated, divided and transfixed at its uppermost aspect, the remainder of the carotid sheath was stripped and the lingual artery, vein and nerve were taken. The dissection was carried medially along the ramus of the mandible, including the facial veins, external maxillary artery, the submaxillary gland with its duct and the lingual salivary glands. All bleeding points were rechecked, and the wound was irrigated with saline solution.

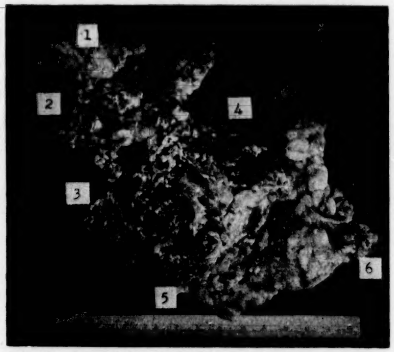


FIGURE 3. *Gross Specimen of Tongue and Neck Tissue Removed at Operation, Showing the Site of the Tumor* (1), *the Digastric Triangle* (2), *the Omohyoid Muscle* (3), *the Cephalic End of the Internal Jugular Vein* (4), *the Clavicular Part of the Sternomastoid Muscle* (5) *and the Posterior Cervical Triangle and a Small Part of the Trapezius Muscle* (6).

Closure of the lower aspect of the wound was accomplished before the lingual dissection was begun. The vertical limb of the wound was approximated with interrupted No. 00 chromic catgut in the platysma and a continuous everting stitch of No. 35 wire in the skin. The area was drained by 2 large Penrose drains emerging from the inferior angle of the wound. A protective dressing was then applied.

Dissection of the extrinsic muscular attachments of the tongue was then carried out. The anterior belly of the digastric, mylohyoid and geniohyoid muscles was dissected, and the genioglossus, hyoglossus and styloglossus were cut at their origins.

Completion of the tongue dissection was performed through the mouth after a stay suture had been placed in the tip of the tongue. The tongue was divided 2 cm. to the right of the median raphe. The incision was carried well beyond the lesion — that is, distal to the vallate papillae and foramen cecum. The tongue incision was developed posteriorly and laterally across the glossopharyngeal arch and then brought forward along the floor of the mouth to the frenum linguae, breaking through the intrinsic and extrinsic muscles of the tongue. The incision was deepened until the entire specimen was delivered en bloc under the mandible into the neck wound, and the radical block dissection was completed with the liberation of smaller vessels and fascia overlying the pharyngeal constrictor muscles. The oral defect was packed with iodoform gauze. The gross specimen of tongue and tissue removed is shown in Figure 3.

The remainder of the skin incision of the neck was closed, and a large pressure dressing applied.

Pathological examination of sections taken in all diameters disclosed complete removal of the lesion. Multiple sections through adjacent tissue and lymph nodes gave no evidence of extension or metastatic involvement. The patient was discharged on the 9th postoperative day after an uneventful recovery. Follow-up examination 4 years later showed the patient alive and healthy, with no evidence of recurrence.

DISCUSSION

There are a few important points that should be made in the surgical consideration of rhabdomyosarcoma and sarcoma of the tongue. Although these are rare they may confront the general surgeon as a problem in lingual tumor. Muscle tumors of the tongue remaining quiescent as an intraglossal lump may give the patient and the physician a false sense of security. Since these tumors in the tongue have tremendous potentialities for sudden growth and metastasis, they should be carefully biopsied. Once a diagnosis of rhabdomyosarcoma has been made the plan of treatment should follow the radical neck and lingual dissection outlined above and the reports in the literature concerning the nature of rhabdomyosarcoma in general.

Experience with oral and lingual carcinoma has demonstrated the feasibility of en bloc resection in the cervical oral region.[18, 38, 39] The operation, like the usual radical neck dissection, begins distally in the supraclavicular and posterior inferior cervical triangles. Progress is then made orad until the stage of suprahyoid dissection has been reached. By now the blood supply to the tongue and mouth has been well controlled. We usually close the neck wound and apply the first layers of dressings before we proceed with the oral dissection to break through the mylohyoid diaphragm to the mouth. This offers excellent access to the entire tongue. We can expose the base of the tongue and the pillars of the tonsils and operate with comfort and security. The surgeon who is accustomed to neck dissections will be pleasantly surprised at the ease with which the radical operation on the tongue can be completed. A large mucosal defect may be covered with a split-thickness skin graft with dental plastic as a stent.

Gordon-Taylor[40] has emphasized the fact that these tumors of the tongue may appear encapsulated. The surgeon may be tempted to do an enucleation or a minor surgical procedure. However, histologically there is no capsule, and these tumors are truly infiltrative. Pack and Eberhart,[12] at Memorial Hospital, New York City, have discussed and outlined in detail the surgical principles of dissection and amputation of rhabdomyosarcomas in the extremities, and these rules can be applied to the tongue. The authors point out that

rhabdomyosarcomas, like other sarcomas, may have multicentric origin in a muscle or group of muscles and may spread along fascial and muscle planes. They have found that the sarcoma involving one muscle will spread directly to an adjacent muscle. Finally, many reports of sarcomas as well as rhabdomyosarcomas of extremities and tongue indicate that there may be lymphatic spread and involvement of regional lymph nodes in 10 to 35 per cent of the cases. In view of these facts the operation of choice seems to be total glossectomy with the combined cervical and oral resection en bloc. This was recommended in the case reported above. However, the patient and the family refused the idea of total tongue resection, and we had to be satisfied with resecting about 65 per cent of the tongue.

An excellent discussion of the use of radiation therapy is found in the article of Pack and Eberhart.[12] Apparently, these tumors are radioresistant. However, only one concerted effort with high voltage radiation has been tried.[33] Preoperative radiation is not recommended; postoperative radiation after a radical resection might be worth while. It seems logical to direct this radiation to the parapharyngeal and retropharyngeal areas with the center of the target about the level of the constrictor pharyngis medius.

We have found that tracheotomy is important in the postoperative management of these patients. When the tracheotomy is done a week or so before operation it offers the anesthetist the possibility of giving the anesthesia through this opening. Preoperatively, these patients should be surveyed from the medical point of view. We have paid special attention to dental and oral hygiene. If the lesion in the tongue is close to the mandible, the periosteum is probably invaded by the sarcoma, since it has been shown in carcinoma of the floor of the mouth that the lymphatics drain through the periosteum in 50 per cent of cases.[18] Therefore, cauterization of the periosteum or total or partial resection of the mandible is indicated. In partial resection of the mandible for carcinoma we have used a stainless-steel prosthesis temporarily. After complete wound healing, this can be replaced by bone.

Prognosis of rhabdomyosarcoma of the tongue is generally unfavorable. As a matter of fact, rhabdomyosarcoma in all parts of the body has been considered a disease with a poor survival rate. However, Pack and Eberhart,[12] using the principles of wide resection and, in several cases, postoperative radiation, reported a five-year survival in 22 patients out of 65. Many of these rhabdomyosarcomas were recurrences. It therefore seems that if the principles outlined above are followed, the average surgeon with experience in neck dissection can hope to achieve a fair degree of success when confronted with a nonepithelial tumor of the tongue, whether it is sarcoma or rhabdomyosarcoma.

Summary

A brief outline of the history of lingual sarcomas in general and of rhabdomyosarcomas primarily arising in the tongue is presented. The rarity and malignancy of true lingual sarcoma and rhabdomyosarcoma of the tongue are pointed out and compared.

A case of rhabdomyosarcoma of the tongue treated by radical surgery and followed for four years is reported. This is believed to be the first reported case of rhabdomyosarcoma of the tongue in which the patient was living and well after more than a brief follow-up period.

Pathological concepts and experience with the natural history of this disease are applied to radical surgical extirpation.

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EXPERIMENTAL PRODUCTION OF CAROTID ANEURYSMS*

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RUPTURE of an intracranial aneurysm is one of the most common causes of sudden death in young adults. The surgical treatment of these "berry" aneurysms has now developed to a stage where knowledge concerning their hemodynamic characteristics is desirable. The present report is concerned with a method of producing "berry" aneurysms of the common carotid arteries of dogs, together with preliminary studies of intra-aneurysmal hemodynamics.

The initial attempts at aneurysm production were by injury to the arterial walls. Incision of the adventitia and media did not cause an aneurysm to form. In the words of John Hunter,[1] who tried this almost two centuries ago, "... the sides of the wound had closed on the artery, and the whole was consolidated to and over it, forming a strong bond of union, so that the whole was stronger than ever...."

Injury to the intima and media, as had been suspected, resulted only in thrombosis. However, we were aware that aneurysm formation was not impossible of attainment, since Shumacker and Lowenberg,[2] in 1947, while studying various methods of end-to-end arterial suture, observed 3 "very small" aneurysms at the suture line in a series of 96 sutured arteries.

Our next attempt was by way of a "vein patch" sutured over a defect in the wall of the common carotid artery. When this was inspected at the end of a week, it appeared that an aneurysm had been attained. However, in spite of weekly exposure of the lesion,§ the process so well described by Hunter proceeded to eventual attenuation of the dilatation within five weeks. With this slight encouragement a successful method was then developed, a vein-pouch graft being used.

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§Hunter[1] cited Cruickshank as having produced an aneurysm as follows: "... after the artery was denuded and thinned, the parts surrounding it were kept from uniting with it, and an aneurism formed...."

METHOD

The common carotid artery and external jugular vein were exposed in the neck of dogs under Nembutal anesthesia. The loose tags of adventitia were removed from both structures, and a suitable length of vein was isolated by clamps and divided close to one clamp. The open end of the portion of vein to be grafted was closed with a continuous arterial suture, and the vein pouch thus produced was excised from the parent vein. Three guide sutures were placed at the open end of the graft. After ligation

FIGURE 1. *Photograph of a "Berry" Aneurysm at the Time of Its Completion (June 10, 1953) in Dog No. 4.*

of the ends of the external jugular vein, rubber-shod clamps were applied to the common carotid artery and a "V" incision made in the artery covering a third of its circumference, with the tip of the "V" pointing in a cardiad direction. The open end of the vein graft was then sutured to the arterial defect, intima to intima, with a continuous, everting mattress suture of fine arterial silk, the suture being anchored several times to prevent excessive constriction of the neck of the vein pouch. The arterial clamps were removed, and any points of leakage

secured by additional sutures. The aneurysm thus produced (Fig. 1) has a palpable thrill, and, if the wall is sufficiently thin, swirling of blood within the aneurysm can be seen.

Results

Five aneurysms have been produced by the method described above. The criteria of patency have included an audible bruit, visible and palpable pulsation on re-exposure of the aneurysms and serial arteriography. The most conclusive evidence was derived from arteriography (Fig. 2). By means of the Fairchild film changer, a series of films were obtained at half-second intervals, before, during and after the open injection of a few cubic centimeters of 30 per cent Urokon into the cardiad portion of

FIGURE 2. *Arteriogram of Seven-Week-Old "Berry" Aneurysm in Dog No. 3.*
The estimated volume of the aneurysm was 304 cu. mm.

the common carotid artery. Our first experimental aneurysm was shown to be patent after five months. However, its estimated volume had increased from 304 to 460 cu. mm. in fifteen weeks.

On the chance that there might be a critical size of aneurysm below which patency would be lost, 3 aneurysms of varying size were prepared upon a single common carotid artery. The smallest of these was patent when tested by arteriography at the end of a week (Fig. 3). However, at eight weeks it could not be identified arteriographically, although its two mates were satisfactorily demonstrated, and direct inspection revealed a small bulge at the site of the "lost" aneurysm.

A few preliminary studies have been made upon the hemodynamics of these experimental "berry" aneurysms. Intra-aneurysmal pressure recordings have been obtained, as well as similar records from the parent artery craniad and cardiad to the aneurysm, with the use of an inductance type of pressure gauge with photographic recording.* Such studies on a week-old aneurysm revealed a striking decrease in the systolic thrust in the parent artery cephalad to the aneurysm, compared to that in the cardiad portion of the artery. This suggested that the thin-walled aneurysm was acting as a relative depulsator upon the systolic thrust in the distal portion of the artery. Support to this thesis was afforded by the presence of a very steep systolic slope in the intra-aneurysmal pressure record. These studies were repeated when the aneurysm was five months old, and the systolic slopes in the artery cephalad and cardiad to the aneurysm and in the aneurysm itself were all essentially equal, suggesting that the buttressed aneurysm did not exert a depulsator effect.

A few determinations have been made on the hemodynamic cycle within these aneurysms, cinefluorographic methods[3] being used.† This technic permits visualization at rates up to 60 film frames per second. Some preliminary impressions were obtained from these films. The velocity in the common carotid artery may exceed 60 cm. per second during arteriography. Flow into the aneurysm appeared in the form of a jet, almost simultaneously with the arrival of the opacified fluid (Thorotrast) at the orifice of

FIGURE 3. *Arteriogram of Aneurysms One, Three and Five Weeks Old, Taken on July 14, 1953, in Dog No. 4.*
The smallest aneurysm was produced one week, the middle one three weeks, and the third five weeks before this arteriogram. The estimated volumes were 17, 207 and 87 cu. mm., respectively.

the aneurysm, but complete aneurysmal opacification did not appear immediately. A swirling motion of the opacified fluid within the aneurysm indicated turbulent flow. De-opacification of the aneurysm occurred at a relatively slow rate.

Discussion

The story of the experimental production of aneurysms covers almost two centuries, beginning with the experiments of Hunter and Cruickshank cited above. The recent report by McCune, Samadi and Blades,[4] adding a very modern touch to the problem, indicates that aneurysm formation followed the injection of nitrogen mustard into an arterial

*Hathaway-type SYB-1 blood-pressure recording system.

†Performed through the courtesy of Drs. W. P. Van Wagenen and J. S. Watson and members of the staff of Strong Memorial Hospital, Rochester, New York.

wall, but these aneurysms all ruptured within three weeks. The most intensive studies on the subject were those of Halsted[5] and his co-workers. After many attempts, they produced aneurysmal dilatation of large arteries distal to constricting metallic bands that reduced the arterial lumen to a third or a fourth of its original size. Halsted stated, "The abnormal, whirlpool-like play of the blood in the relatively dead pocket just below the site of the constriction, and the lowered pulse pressure may be the chief factors concerned in the production of the dilation."

Although the present report is concerned chiefly with what appears to be a satisfactory method of producing experimental "berry" aneurysms, the ultimate objective is the study of intra-aneurysmal hemodynamics. Freeman[6] reported observations on intra-aneurysmal pressure in a series of clinical cases. However, theoretical hydraulics indicates that the following stress factors must be considered as potential sources of strain to an aneurysm[7, 8]: total hydrostatic pressure, pulsatile flow, turbulence and jet action. It is anticipated that further data upon these factors may be obtained from appropriate studies on aneurysms experimentally produced.

Summary

A method for the experimental production of aneurysms of the common carotid arteries of dogs, utilizing a vein-pouch graft, is described. Persistent patency of these aneurysms was demonstrable after a considerable period, but there may be a factor of critical aneurysmal size. Studies of intra-aneurysmal hemodynamics are reported in preliminary form.

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MEDICAL PROGRESS

MATERNAL AND CHILD HEALTH

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MATERNAL and child health services are organized public efforts, governmental and nongovernmental, to promote and protect the health of mothers and children. The clinical basis of maternal and child health derives to a great extent from pediatrics and obstetrics, and its scope and effectiveness have been enhanced by the increasing emphasis on preventive medicine in these specialties. Reviews of preventive medicine in these special fields in 1942[1, 2] and 1953[3] provide an indication of progress during the past decade and of changes in point of view and emphasis that reflect the ebb of some problems and the rising tide of others.

Recent advances in pediatrics and the status of certain current problems of major interest were discussed by Baty, Kreidberg and Swenson[4] in 1952. In the preceding year Smith[5] reviewed the development of pediatrics and described the early development and subsequent growth of the "child health movement," as well as the responsibilities in planning, financing and execution of child health services assumed by private organizations, medical societies and the Government. Tenny[6] reviewed advances in obstetrics, discussing the significance of appropriate prenatal diet, the question of abortion and a number of problems of pregnancy and labor. Hand in hand with progress in the basic clinical branches, and with increasing attention to prevention, private organizations and public agencies have been advancing the application of these developments in knowledge, through organized programs of maternal and child health. Twenty years ago, Harold C. Stuart presented a critical appraisal of maternal and child health that reviewed progress and foreshadowed many of the subsequent developments. Following Stuart's outline, this report presents a review of advances in maternal and child health services and of significant contributions of governmental and nongovernmental organizations to extension and improvement of such services.

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The Field of Public Health

Maternal and child health services form a functional division of the total program of public health. Progress in public health during the past twenty

years has obviously had much to do with both the possibilities and limitations of maternal and child health.

In the year before the appearance of Stuart's review, the American Public Health Association established a standing committee on professional education. Largely under the leadership of this committee, the standards of education and experience for public-health workers have been set up, 11 graduate schools of public health have been accredited, and accredited field training areas for public-health residencies have been established. A specialty board, certifying physicians qualified in preventive medicine and public health, was formed in 1949, on the initiative of the Professional Education Committee of the American Public Health Association and the sections on Preventive and Industrial Medicine of the American Medical Association. Public health has "gradually, and rather recently . . . emerged as a profession."[7] Increasingly, with the growth of schools of public health, trained specialists, physicians and others are tending to replace the untrained in public-health agencies.

A distinguishing feature of public health is its characteristic use of members of various basic professions for joint attack on common problems. Medicine, dentistry, veterinary medicine, nursing, social work, education and other professions are involved, and specialists in the physical, biologic and social sciences are required. The skills of these varied groups are joined in an organized force under the leadership of an expert in public-health administration. Although the part-time lay health officer has not entirely disappeared, fully organized and well staffed health departments are essential for the full application of current scientific knowledge to contemporary problems. More than two thirds of the population of the United States is living in areas served by local health departments — more than twice the proportion of 1922. The lack of local health departments for a third of the population is one of the chief limitations on public health in general, and of course on maternal and child health as well.

Contributors to Progress

This has been a period in which many of the demonstrations and experiments, originally sponsored by foundations and private organizations, have become firmly established as normal responsibilities of public-health agencies, especially of state departments of public health and of local health agencies.

Under the stimulus of the Sheppard–Towner Act (1921–1929), the first national grant-in-aid program for health purposes, virtually every state created a division of maternal and child health services. The Social Security Act of 1934 initiated grants-in-aid to states for general public-health purposes, and resumed specific grants for maternal and child health, adding crippled children's services and child welfare. These programs have helped, through the matching principle, to increase in quantity and quality the preventive services provided through state public-health agencies, providing technical services to the agencies and stimulating improved professional training of health-department staff members. The lessons learned through experience in one area are quickly brought to the attention of others by means of the regional consultation programs of the federal agencies concerned with health.

In the specific field of maternal and child health, a large measure of leadership has come from the United States Children's Bureau. Its work over the past forty years has encouraged research, fostered mutual understanding and co-operation between social and health services and sponsored co-operative activities of child health organizations with school systems, private organizations and the medical profession. In four decades, the Children's Bureau has had only four chiefs, each a leader in the development of child health and welfare services. The United States, it is believed, was the first country to establish by Congressional act a major governmental agency concerned with "all aspects of child life." Certain aspects of specific programs have at times been the subject of disagreement, but there is wide respect for the Children's Bureau, and in general a high measure of co-operation between the Bureau and the medical and other professional organizations. Among the general public, there is much interest and popular support for the Children's Bureau.

The American Academy of Pediatrics has been an important factor in advancing and improving child health services. Its report on child health services and pediatric education,[8] based upon a nationwide study in which the United States Public Health Service and the United States Children's Bureau co-operated, provided a fund of valuable information concerning all aspects of child health services furnished in private practice and through public services. The separate state reports, which afford further detailed data for most of the states, give evidence of a widespread interest and extension of all aspects of child health services, but many deficiencies as well. Among other things, uneven distribution of medical care and health services for children was pointed out, inadequacies in well-child supervision and school health services were described, and a lack of outpatient and medical consultant services for children in more isolated areas was noted. Insufficient development of education in pediatrics, especially in the preventive aspects, was one of the important findings. This applied to undergraduate medical education, house-officer training and postgraduate medical education.

This study and the follow-up work that has thus far resulted from it are in accord with the sense of responsibility for helping to assure the application

of sound principles of child health that the Academy expressed from the time of its organization. Continuing activities in the spirit of the study of child health services may be expected to stimulate and guide further advances in improved services. Morse,[9] in his presidential address of 1932 said, "It is one of the functions of the Academy to see that physicians take an active interest in the child welfare movement and that they take their proper place in it." He expressed full agreement with Stuart's recommendation to the Massachusetts State Committee: "That the committee attempt to cooperate actively with the state department of health, as well as with other organizations similarly minded, in efforts to improve the child health service available throughout the state, in making it available in those communities where there is no adequate service at present, in passing upon the medical desirability of plans prepared by these organizations, and in seeking the cooperation of practising physicians in plans that are acceptable." The recent establishment of the American Academy of Obstetrics and Gynecology promises a comparable interest in the preventive aspects of maternity care.

The fifth in the series of decennial White House Conferences on Child Health was held in 1950.[10] This conference was noteworthy for participation of lay and professional members in informal discussion meetings as well as formal sessions. Mental health formed the theme of the conference, and all aspects of maternal and child health were explored and discussed from this point of view. Just as the 1930 Conference had assembled available expert opinion and factual knowledge concerning child health and growth and development, and stimulated interest and progress in these fields, the 1950 Conference should prove fruitful in advancing services and research concerning the mental health of children.

Two developments within the United Nations mark important advances of maternal and child health in the post-war period. One is the establishment of the United Nations International Children's Emergency Fund (UNICEF). The other is the creation of a Maternal and Child Health Section of the World Health Organization (WHO) and its regional offices. UNICEF, formed December 11, 1946, has provided aid for mothers and children, first in an emergency food supply program and subsequently in plans for support for medical and health services and professional education. The number of UNICEF-supported programs reveals the geographic scope and comprehensiveness of child health activities sponsored by governments to which that organization has given assistance.[11]

Close co-ordination is maintained with the Maternal and Child Health Section of the World Health Organization on technical aspects, recruitment of personnel and evaluation of goals. Among other services provided by the Maternal and Child Health Section, advisory groups of experienced personnel from many countries have developed for the World Health Organization a technical-report series, which serve as advisory documents providing technical guidance in program planning. A number of such reports covering prematurity, maternal health, services for school children and several related subjects have appeared.[12]

The Philosophy of Public Health

Stuart noted, in 1933, that "the former purpose of attaining the health of the masses by the use of mass methods has been extended to one of controlling preventable diseases and disabilities in individuals by means of contact with and services for them. The former required little or no individual initiative, while the latter requires an understanding cooperation." These changes, he believed, had largely grown out of and were clearly demonstrated by services for children.

The further evolution of this concept has led to the conviction that personal health services range from promotion of health, chiefly educational, through specific disease prevention, prompt diagnosis and treatment to prevent or limit disability, and rehabilitation. In this spectrum of services, the needs and characteristics of individuals become more and more important. Increasing emphasis is placed on pattern and variation in growth and development, the formation and evolution of psychologic characteristics and the force of social factors on individual and family development. In maternal and child health, studies of families and individuals in relation to several types of problems have been reported or are now in progress.

The advances in detailed knowledge of growth and development based upon longitudinal studies over the past two decades have laid a firm basis for health supervision in infancy and childhood. Major principles, now well established, are that children tend to follow well defined patterns of growth and development. The variation of pattern among different children is well marked, and deviation of a child from his own pattern is an indication for investigation of physical, nutritional or psychologic factors that may be responsible. Utilization of tables of average height, weight and other physical measurements to classify children on the basis of single observations has distinct limitations. Much more useful are growth records for charting the progress of individual children, so that deviations from their own trend of statural and weight progress may be readily recognized.

Maternal and Child Health Services

The basic subdivisions of maternal and child health services are for maternity and newborn care, as well as programs for infants and preschool children, children of school age and handicapped children. Within this framework certain subjects may be singled out for special comment.

Maternity and Newborn Care

The concept of maternity care has come to embrace all factors concerned with the health of the childbearing woman and her infant. It is thought of as beginning with the protection of health of the baby girl and continuing through childhood and youth, into the reproductive period, and even into later life.[13]

In the narrower sense of the actual care of the pregnant woman, thorough investigation into the state of physical health is supplemented with education and what has been termed coaching and preparation for delivery and care of the new baby. Such individual and personal guidance must take into account social and emotional as well as physical factors that may affect the pregnancy and delivery. It need not be emphasized that individualization of care takes time. In clinic services inadequate staffing sometimes precludes a reasonably good standard of care. Moreover, several investigations have shown that too many women do not begin prenatal care until late in pregnancy.

Understanding of nutritional requirements in pregnancy has been greatly advanced by investigations of both animals and human beings.[14]

The contributions of Dieckmann et al.[15] and Burke and her collaborators[16] have provided evidence that there is a close relation between diet and complications and outcome of pregnancy. In general, good diets, which include a high intake of protein, are associated with a decreased incidence of toxemia and an increased proportion of infants in good condition at birth. Studies recently reported[17] discuss the size and content of fetal liver in relation to maternal diet in a manner similar to the findings of Wallace in animals. It is possible that the state of nutrition of women before conception plays a part in the course and outcome of pregnancy. Preconceptional food habits appear likely to establish the eating pattern, which tends to be followed with little variation during pregnancy.

The advice to be given depends upon careful review of the diet of each patient, so that the recommendations can be adapted to the previous dietary history and nutritional status, and also to food habits and attitudes. These long-established food habits are difficult to change.

To provide the motivation without which little success can be expected, nutritional advice must be individual and personal, rather than general. It requires not only sound basic knowledge of nutrition, but also skill and experience in interpreting the reasons for necessary food changes to patients. To this end, nutrition services are being added to programs of prenatal care, and nutritionists of health departments and voluntary agencies provide both service and consultations to physicians and public-health nurses in prenatal clinics. In private practice the responsibility is generally borne alone by the physician. Some physicians are finding that public-health nurses provide a valuable auxiliary service in this and other respects. Classes for mothers are also helpful.

Epidemics of diarrhea of the newborn, of which a number were reported in the 1930's and early 1940's, brought into serious question the wisdom of the use of large congregate nurseries in maternity services. At the same time advantages to the mother and infant when the mother was permitted to have her infant near her during the post-partum period were pointed out. Both factors led to an interest in so-called "rooming-in" plans — essentially an adaptation of the practices in effect before newborn nurseries were instituted. In 1950 it was reported that more than 40 hospital services offered such arrangements at least for some of their patients.[18] The psychologic and educational objectives, as well as protection from infection, are facilitated by suitable physical arrangements. George Washington University Hospital was the first to provide a specially planned facility constructed specifically for rooming-in.[19]

Progress in research on the causes of congenital malformations has been considerable. Genetic mechanisms, physical, chemical and biologic agents have been identified among causative factors in animal experiments and, to a more limited extent, in observations on human beings.[20-22]

There is, at present, no proof that specific nutritional deficiencies cause congenital anomalies in the human being as they have been shown to do in animal experiments. Nevertheless, in view of the implications of animal studies, as well as for reasons previously referred to, prudence dictates careful attention to the provision of optimal diets during pregnancy. In addition efforts to prevent the occurrence of rubella in pregnant women (by deliberate exposure of girls during the school age, or possibly by use of gamma globulin prepared from the serums of patients convalescing from rubella) merit consideration. No doubt, as research in the etiology of congenital malformations advances, a number of preventive measures will become available.

Congenital syphilis has shown only a moderate decline in the number of reported cases and in the rate per 1000 live births during the past decade. The disease is, of course, preventable, almost without exception, provided that serologic examination of pregnant women is appropriately carried out. Since an effective therapeutic agent is now available the problem is one of assuring prenatal care to all pregnant women.[23]

Studies of maternal mortality, which are generally conducted by special committees of state medical societies in co-operation with state departments of public health, have made important contributions to the reduction in maternal mortality. The method of careful study of all maternal death

records permits the identification of preventable factors.[24, 25] Recommended procedures for the first studies were worked out by the late Dr. Robert L. DeNormandie,[26] who was chairman of the Obstetric Advisory Committee of the United States Children's Bureau.

The significant decline in maternal mortality that began in the 1930's has continued throughout the past decade, the rate decreasing from nearly 40 maternal deaths in 1940 to less than 8 per 10,000 live births in 1950. Recent reports from maternal-mortality committees show that, despite this enormous reduction, a major share of the deaths currently occurring are still preventable. The Committee on Maternal Welfare of the Massachusetts Medical Society,[27] for example, classified 20 of the 35 deaths as preventable.[28, 29]

A similar report from downstate Illinois[30] classifies 17.5 per cent of the 297 deaths in that state during the period 1948–1951 as preventable, and 62 per cent as having preventable factors. The quality of prenatal care among these patients, according to the standards of the American Committee on Maternal Welfare, was found to be poor or absent in 38.4 per cent and "adequate" in less than a fifth. Hemorrhage, toxemia and infection remain among the leading causes, although unequally so in different areas. Attention has recently been called to deaths from aspiration of vomitus during anesthesia in obstetrics, which is estimated to account for 2 per cent of all maternal deaths.[31]

Infancy and the Preschool Period

There has been little change in the fundamentals of health supervision during infancy and the preschool period. Periodic, carefully performed medical examinations (including, of course, detailed histories obtained by unhurried interview with the parent) still form the basis for assessment of growth and development and of nutritional status, early detection of evidence of chronic disease or physical handicap or impairment of the organs of special sense, and appropriate attention to mental and emotional development.

The Study of Child Health Services of the American Academy of Pediatrics shows that pediatricians devote a major share of their time to well-child supervision, general practitioners giving a smaller but still significant portion of their time. Child-health conferences (well-baby clinics) provide only about a tenth of the total well-child care.

The most striking change in infant feeding is the present rarity of maternal breast feeding. The only available nationwide data, limited to the feeding status of infants at the time of discharge from the hospital,[32] show that 70 per cent of hospital-born infants are never offered the breast or are fully weaned from it by the end of their hospital stay. Data from the Whittier Street Health Unit in Boston show that only 15 per cent of infants seen in the well-baby clinic are still exclusively breast fed at one month of age.

This enormous decline in the incidence of breast feeding has occurred in about thirty years, for the limited data then available indicated that, among private patients, approximately 80 per cent were breast fed for six months or more. Whatever the factors underlying this marked change, and they are far from clear, it is obviously a subject for research, which should contribute to a more precise knowledge of factors influencing the maternal-infant relation.

The limited clinical experience of most physicians and nurses with the management of normal and disturbed lactation is unfortunate, since mothers who desire to nurse their babies sometimes receive little guidance based on physiologic considerations[33] and little encouragement. Understanding of the psychologic mechanisms and effects involved also seems to be inadequate. Investigations of mother and infant and, perhaps equally important, of the formation of attitudes in fathers, physicians and nurses are clearly warranted.

There has been a distinct trend toward earlier feeding of solid foods in the form of purées during the first months. Various solid foods are now more or less regularly offered at two months or even one month of age. A reasonable variety of such foods accustoms the infant to the ingestion of solids and affords protection against specific nutritional deficiencies — for example, of iron.

The rigid and inflexible infant feeding schedules characteristic of the 1920's were challenged in principle by Clara Davis's[34] well known studies and by Brenneman's[35] brilliant paper based on his own acute clinical observations. In September, 1938, the simple, human, but clinically exact discussion of infant feeding presented by Aldrich and Aldrich[36] appeared. Nevertheless, a standard textbook as recently as 1940 still spoke of "training" the large majority of infants to take feedings at four-hour intervals "from the beginning."[37]

The tendency to greater flexibility, however, is now general. The overenthusiastic and sometimes unthinking recommendation of this feeding procedure bears a certain risk of exaggerating the lack of self-confidence manifested by some mothers, especially those of first babies. For such mothers a judicious outlining of a reasonable schedule with definite but not inflexible advice on quantities and intervals is helpful.

The recognition of the physiologic decrease in appetite, which commonly occurs in the second year of life, and advice to mothers based on this developmental characteristic have undoubtedly contributed to a decrease in feeding problems among preschool children. An important corollary is that the caloric requirements during the phase of slow growth from the second to the fifth year are so limited that careful planning of the diet is necessary to assure that the essential nutrients are adequately supplied.

At the beginning of the 1940's pertussis vaccine and tetanus toxoid were available, but experience had not yet become sufficiently extensive to permit them to be unequivocally recommended for routine use. Moreover, combined antigens had been introduced by Ramon[38] in 1936 and had not yet gained universal acceptance.

Although effective immunizing agents against smallpox and diphtheria were, of course, available, many persons were not being immunized, as evidenced by 10,000 reported cases of smallpox in 1939, and 30,000 reported cases of diphtheria in 1938, with 2600 deaths from diphtheria.

At present, immunization early in infancy against diphtheria, tetanus and pertussis by means of combined triple antigen is a thoroughly established procedure. The literature has been reviewed by Lapin.[39] Booster doses of the same combined antigen are recommended up to school age. The recent development of a diphtheria toxoid with two flocculation units per cubic centimeter will probably permit the administration of effective, small, booster doses of combined diphtheria and tetanus toxoids to persons over ten years of age without the unpleasant reactions that may result from the usual diphtheria toxoid.

As for passive prophylaxis, gamma globulin has replaced placental globulin and other agents formerly used for the prophylaxis of measles, and it is especially indicated in infants and in children suffering from concomitant serious illness.

Recently, attention has been given to the use of gamma globulin as a possible prophylactic agent against poliomyelitis. Although of interest, the procedure seems to offer little as a method for controlling that disease in the future. On the contrary, the important developments in culturing and typing the viruses of poliomyelitis and work in progress on vaccines prepared from virus hold promise of a means for widespread active immunization perhaps within the near future.

Although interest in BCG continues and programs of BCG immunization in many countries have been carried out on unprecedentedly large scales, there is no convincing reason to believe that the procedure is applicable as a public-health program in the United States today.[40] However, its use may be justified in individual situations when, despite all efforts, protection of infants and children who are tuberculin negative from exposure to tuberculous infection cannot be assured with certainty.

With safe and effective antigens, standard immunization programs for protection against smallpox, diphtheria, pertussis and tetanus have been worked out, and should be uniformly carried out for all infants and children, except in the presence of contraindications — for example, eczema as a contraindication to smallpox vaccination and a history of convulsions as a contraindication to pertussis vaccination.

Children of School Age

There has been considerable change in the attitude toward health services for school children and, to some extent, a change in practice as well. Among those who plan and direct such services, there is great emphasis on the need to abandon sterile routine "periodic physical examinations." In their place physicians serving schools are expected to assume the responsibility for promoting the use of private physicians and public facilities for medical care by the pupils, of developing the abilities and resourcefulness of teachers for "health observation" and referral of pupils and of effectively utilizing the services of public-health nurses. The physicians in school systems are also expected to play some part in promoting the healthfulness of the school environment, physical and social, and in working closely with teachers and guidance specialists in fostering mental health.[41]

Unfortunately, although some school systems show progress in adapting and modernizing health procedures, many are still on a highly routinized, impersonal and not too effective basis. Better compensation, smaller case loads and more status for physicians working in school health should improve the situation. However, problems of policy that call for solution remain. Among them are that of providing care for school children as a part of their family group rather than separately from it, that of integrating health supervision with medical care during illness and that of improving the capability of schools to serve handicapped children educationally, socially and in accordance with their health and medical needs. The marked interest and activity in mental health in schools is obviously a response to a recognized need.[42]

Health services for children in secondary schools, characterized as "backward" twenty years ago, have made headway. School health services are now giving increased attention to both the developmental aspects and the health needs of adolescents.

Handicapped Children

Epilepsy. The greatly increased possibility of control of seizures that has resulted from the introduction of new therapeutic agents and the advances in diagnostic methods, and understanding of social and psychologic aspects of epilepsy have given new emphasis to this group of conditions. Because of the increasing number of therapeutic agents, with their specific characteristics and side effects, selection of the appropriate one must be based on a complete appraisal of the individual patient, including determination of the precise type of cerebral dysrhythmia present, and dosage must be carefully adjusted.

The related personal and family problems, social and psychologic, which are common in children with epilepsy, the acceptance of the child in a regular school or, for a minority, arrangements for other

forms of education and training, vocational training and placement are some additional aspects of the complex problem of total care intended to minimize the handicap and promote maximum social adjustment. The individual practitioner provides the supervision of specific therapy, but, increasingly, specialized centers are developing that afford complete diagnostic resources and the essential related services, as well as consultation and programs of professional training.

Hearing impairment. The advent of chemotherapy and antibiotics has reduced the incidence of impairment of hearing resulting from middle-ear infection. However, extension of systematic programs of audiometric testing of apparently normal children indicates that many of the children who, at school entrance, have hearing impairment have not previously been tested, and may never have been suspected of not hearing normally. Such children lack the learning experiences of those whose hearing is normal, and they are less educable at school age. Behavior difficulties are not uncommon, and some may have been incorrectly considered to have been mentally retarded.

Well developed plans of care for preschool children whose hearing is impaired result in more mature, more educable children who enter school. Such programs include diagnosis of the cause of the hearing impairment and whatever therapy is indicated, estimate of the nature and type of hearing loss, provision of suitable hearing aids if needed and auditory training, speech reading, individual and group learning experiences and social and psychologic services.

Other conditions. For children with orthopedic and neurologic conditions, more emphasis is being placed on treatment and education plans that tend to maintain the child within the family group, in his own home as much as possible. Resort to institutional care, although unavoidable for many, is less frequent than formerly. Efforts are being made to shorten the duration of necessary hospitalization and to reduce the effect of separation from family so far as possible.

This is the tendency in hospital and institutional care not only for handicapped children but also for children in general, after many observations (recently summarized[43]) suggesting that separation from family, especially from the mother at certain periods of childhood, may be involved in psychologic disturbance. There is interest in extension of programs of home medical care and increased availability of ambulatory services (both for diagnosis and for therapy) especially in rural areas, somewhat similar to those of existing "crippled children's clinics." Liberalized visiting hours and revision of hospital admitting procedures and other routine practices are being studied in several centers in an effort to prevent psychologic disturbances from hospitalization.

Other situations involving children in temporary or long-term separation from mothers are receiving increased attention. Fewer children are now in public institutions because of dependency, neglect or delinquency, but it is probable that with improved social and health services and their better co-ordination, the number of institutionalized children can be further reduced.

Children Away from Home

A marked expansion of facilities for daytime care of children away from their own homes occurred during World War II. Because of the hazards to health from the grouping of children of preschool age, health departments became interested in establishing standards for health and safety. Although the licensing authority for such day-care centers is more often placed in welfare than in health departments, the latter are frequently involved in co-operation or consultation with the licensing agency.

Discussion

There is no need to summarize the great advances in reduction of maternal, fetal and infant and child mortality, and in reduction in morbidity from a number of specific conditions. Graphic presentation of some of the data is conveniently available in a publication of the 1950 White House Conference.[44]

Among current problems on which interest centers are prematurity, congenital malformations, accidents and the broad question of mental health in all its aspects. The gross differences in mortality and morbidity rates among different groups of the population living in the same area and differences in the amount and type of medical care and health services that mothers and children of different social and economic groups receive pose concrete and practical problems for investigation and administrative action in public health.

Physicians administering maternal and child health services have a direct influence on the extent and quality of the programs of care in their areas. They set minimum standards for institutions and services, purchase and pay for hospital and medical care on the basis of specified types of service, finance and organize programs of consultant service and postgraduate education, provide means for education of the public in maternal and child health practices and conduct, or co-operate in, various forms of research in their fields.

The only brake on further progress comparable to that achieved in the past is that of underfinancing and understaffing.

Dublin's[45] statement, made in Boston over twenty years ago, may still be pertinent:

> Health departments in our country have never suffered from inflation. Health officers have always been notoriously underpaid. Our health personnel has not been over extended. Therefore, in these times of stress, such contraction as is possible in other services is not possible here and it is poor policy indeed to save pennies and thereby throw out of gear services which conserve life and health. . . .

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MEDICAL INTELLIGENCE

NECROSIS FOLLOWING INTRAVENOUS USE OF NEO-SYNEPHRINE*

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INTRAVENOUS administration of arterenol (levophed or nor-epinephrine) has been reported to cause tissue necrosis. This has occurred both with and without extravasation.[1-4] The purpose of this paper is to report 2 cases that followed the intravenous use of Neo-Synephrine Hydrochloride as a pressor drug postoperatively. A search of the literature has revealed no similar cases.

FIGURE 1. *Sharply Demarcated Necrotic Lesion in Case 1, Overlying the Greater Saphenous Vein about One Month after Neo-Synephrine Extravasation.*

Case Reports

CASE 1. A. H., a 52-year-old Negro, was admitted to the hospital for treatment of malignant hypertension. On November 21, 1952, a left thoracolumbar sympathectomy was performed by a transthoracic route. To combat hypotension on the day of operation Neo-Synephrine, 20 mg. per liter, was infused intermittently via a polyethylene catheter, 0.16 cm. in outside diameter, inserted by cut-down into the greater saphenous vein at the right ankle. On the following morning it was noted that there had been extravasation of the infusion. By evening the patient was complaining bitterly of pain at the site of infiltration. During the next 9 days a flame-like area developed that vesiculated and then formed a firm eschar (Fig. 1). The area was grafted on January 16, 1953. On excision of the slough it was seen to involve skin and subcutaneous tissues.

It is of interest that this patient had a thoracolumbar sympathectomy on the right on December 1, and again received Neo-Synephrine by catheter intravenously for two days, without infiltration or reaction.

CASE 2. V. A. C., a 39-year-old woman with severe mitral stenosis and auricular fibrillation, was admitted to the hospital for surgery. On April 7, 1953, valvulotomy was performed. On the following day because of hypotension, Neo-Synephrine, 20 mg. per liter, was added to an infusion already being given through a Rochester plastic needle, inserted percutaneously into the greater saphenous vein at the left ankle. Because the infusion was running poorly, the bottle was elevated. Within an hour infiltration occurred. An area of blanched skin about half the size of the palm of the hand was noted, and the patient complained of local pain. The needle was removed, and the infusion containing the Neo-Synephrine was continued intermittently in the left arm without difficulty for several days. On April 9 the previously blanched area on the left leg appeared mottled. Two days later tissue-oxygen measurements indicated that the discolored area was probably necrotic (Fig. 2*A* and 3). Severe pain lasted at least 5 days. On May 4, 1953, the defect was excised and grafted. This area of necrosis involved the skin and subcutaneous (Fig. 2*B*) tissue as in Case 1.

Discussion

Neo-Synephrine has been widely used intravenously to combat hypotension, especially after operation. Its subcutaneous use has also been recommended. Apparently, as with that of arterenol, its administration is not without risk, and this may be true for other strongly pressor drugs. In the cases reported above, Neo-Synephrine administered in reasonable concentration resulted in marked tissue necrosis. The full sequence of events took several weeks and included almost immediate blanching, followed in twenty-four to forty-eight hours by mottling and vesiculation. Subsequently, a firm

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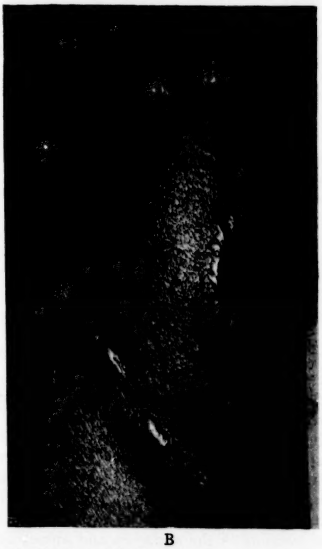
eschar slowly formed. Pain was a significant factor in each case and of sufficient intensity to overshadow the incisional pain of a thoracotomy. In both cases the reactions followed obvious extravasation, but the literature on arterenol indicates that this may not be essential. Unfortunately, although the chance of extravasation is reduced by the use of a polyethylene catheter or plastic needle this precaution does not ensure against its occurrence and great care should be taken to determine that plastic needles and catheters are working perfectly before pressor drugs are given. Because of frequent extravasation regular needles should not be used for prolonged infusion of these substances. The subcutaneous administration of Neo-Synephrine, at least in extremities, should be abandoned.

A



B

FIGURE 2. *Case 2. Necrotic Lesion (4.5 x 9.5 cm.) after Neo-Synephrine Extravasation.*

A = appearance after three days, showing blister formation and discoloration. Oxygen-tension measurements indicated actual necrosis. B = appearance at twenty-six days; a firm eschar is present.

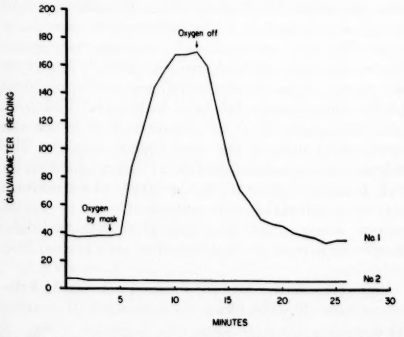


FIGURE 3. *Electrodes in Normal Skin, Showing Normal Marked Response to Breathing Oxygen (No. 1).*

In the discolored area shown in Figure 2A, electrodes demonstrated no response to oxygen, indicating severe ischemia or necrosis (No. 2).[4]

SUMMARY

Two cases of local necrosis after extravasation of intravenously administered Neo-Synephrine are presented. This reaction appears to be substantially identical to although less extensive than that after extravasation of arterenol.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40031

PRESENTATION OF CASE

First admission. A forty-five-year-old woman entered the hospital because of dyspnea and abdominal swelling.

At the age of seven the patient had had rheumatic fever, after which she had a persistent heart murmur. There were no further frank attacks of rheumatic fever, but she had aching joints intermittently. Four years before admission shortness of breath, orthopnea and swelling of the abdomen and ankles developed. She had had known hypertension with a systolic pressure as high as 250 for the past three years. There had been no albuminuria or urinary symptoms. She had occasional headaches. Digitalis preparations had been taken irregularly. She had been unable to work for the eleven months before admission and for two months had been a semi-invalid. There was no history of recent fever.

Physical examination revealed a well nourished woman in no acute distress. Ophthalmoscopic examination showed minimal arteriolar narrowing. Medium fine moist rales were heard at both lung bases. A heaving cardiac apical impulse was felt 2 cm. within the left anterior axillary line, and the mitral first and pulmonic second sounds were accentuated. A Grade 3, harsh, apical systolic murmur transmitted to the axilla and a Grade 2, early, apical diastolic rumble were heard. The neck veins were distended and pulsating. A slightly tender liver edge was felt almost to the iliac crest extending across the epigastrium. A firm, tender tip of the spleen was palpable in the left upper quadrant. There was bilateral pitting edema of the ankles. There were no petechiae, and no clubbing was noted. The left shoulder joint was painful on motion.

The temperature was 96°F., the pulse was irregular, with a rate of 160 at the apex and 120 at the wrist, and the respirations were 25. The blood pressure was 200 systolic, 130 diastolic.

Urinalysis was negative. Examination of the blood disclosed a hemoglobin of 15.3 gm. per 100 cc. and a white-cell count of 13,250; the nonprotein nitrogen was 24 mg. per 100 cc. The sedimentation rate was 0.4 mm. per minute. Two stool specimens were guaiac negative. Fluoroscopic and x-ray examination of the chest demonstrated a grossly enlarged heart with a cardiothoracic ratio of 18.5:29. There was no congestion of the pulmonic vascular shadows. A film of the left shoulder was normal. An electrocardiogram showed auricular fibrillation, with a ventricular rate of 75, a QRS interval of 0.07 second and slight left-axis deviation. The T waves were upright in Leads V_2 and V_4, low in Leads 1, 2 and 3 and diphasic in Lead V_6. A blood culture was negative.

Digitalis was given, with improvement in symptoms, and the patient was discharged on the tenth hospital day on a cardiac regimen.

Final admission (5 years later). She continued to have dyspnea and orthopnea requiring two pillows for relief. Within a year of discharge the blood pressure was 150 systolic, 90 diastolic, and it remained at this level. Eighteen days before admission she noted fleeting, shooting pains in the upper abdomen. Three days later she had a steady, increasing back pain radiating around the iliac crests and to the suprapubic area. The pain was excruciating and unaffected by position. A week before admission she had severe pain in the upper anterior portion of the abdomen that gradually subsided. She felt very weak and nauseated. For the ten years before admission her menses had been irregular, the last menstrual period having occurred six months before admission.

On physical examination the heart was enlarged, the border of dullness extending to the left. There was auricular fibrillation. The pulmonic second sound was softer than the aortic. The previously heard Grade 3, apical, systolic murmur was noted. There was no audible diastolic murmur. The chest was clear except for slight dullness and diminished breath sounds at the left base posteriorly. The liver edge was palpable three fingerbreadths below the right costal margin and was slightly tender. The splenic tip was again palpable. There was ascites as well as marked generalized tenderness of the abdominal wall; peristalsis was normal. On pelvic examination a soft cystic mass was present in the right iliac fossa just above and lateral to the external iliac pulsations.

The temperature was 97°F., the pulse 90, and the respirations 20. The blood pressure was 110 systolic, 80 diastolic.

The urine had a specific gravity of 1.010 and gave a + test for albumin. The hemoglobin was 15 gm. per 100 cc., the white-cell count 13,100, and the nonprotein nitrogen 88 mg. per 100 cc. An electrocardiogram revealed auricular fibrillation with a ventricular rate of 95, a QRS interval of 0.08 second and

a normal axis; the T waves in Leads 1, 2 and 3 were inverted as compared with the previous tracing, and the R waves in Leads V_1, V_2, and V_3 were absent. A roentgenogram of the chest did not reveal any changes. In some roentgenograms of the abdomen a large soft-tissue mass was visible in the midline of the pelvis, whereas in others it was not seen or was not very prominent. An intravenous pyelogram and cystogram, a gastrointestinal series and a barium-enema examination were negative. Cystoscopy was unremarkable. A blood culture showed no growth.

The patient's general condition remained about the same until the thirtieth hospital day, when substernal pleuritic pain developed. Physical examination revealed an expiratory leathery friction rub over the anterior lower right side of the chest. There was no cough, hemoptysis or fever. The chest pain subsequently diminished, but she had dull abdominal pains and an intermittently distended abdomen with tympany and active peristalsis as well as anorexia. The nonprotein nitrogen fell to normal limits with electrolyte therapy. On the forty-sixth hospital day an operation was performed.

Differential Diagnosis

Dr. Earle M. Chapman*: When this woman was forty-five years old she was hospitalized with symptoms that clearly depicted rheumatic heart disease with mitral stenosis and insufficiency associated with hypertension. Evidently, for eleven months she had been in severe congestive heart failure with a huge, fibrillating heart, pulsating, bulging neck veins, a large liver and spleen and edema of the ankles. Active rheumatic fever was suspected. Subacute bacterial endocarditis was considered unlikely since only one blood culture was taken. When, at the age of fifty, she returned with the story of respiratory limitation imposed by the rheumatic heart disease, the electrocardiogram suggested that she had at some time a myocardial infarction of the anterior wall. Although she had ascites there is no note that the veins were engorged; distention of the neck veins is one of the most valuable clinical signs of congestive heart failure that we have. Rather, the problem now seems to have centered in the abdomen, for she had shooting pains in the upper part of the abdomen eighteen days before entering the hospital; this pain was described as excruciating, and the week before entry it was severe. Pelvic examination revealed a soft cystic mass that was outlined on the x-ray films.

May we see the x-ray films?

Dr. John F. Gibbons: The chest films made at the time of the first entry demonstrate that the heart is grossly enlarged and the left main bronchus is elevated, indicating enlargement of the left atrium; the double shadow of the enlarged left atrium is visible through the main heart shadow. There is no evidence of pleural fluid or pulmonary vascular congestion. The vessels in the lungs are of normal caliber, and the lungs are clear. Five years later there has been a marked change in the size and configuration of the heart, again without evidence of failure but with some evidence of enlargement of the left atrium in the right oblique projection. The marked decrease in size in the five years without evidence of failure at either time suggests that she had a pericardial effusion at the time of the first admission. A pyelogram taken during the second admission shows normal excretion, normal appearance of the renal collecting system and a normal-looking bladder shadow, above which is the rounded density projecting over the bony pelvis. I think we ought to mention that sometimes we are deceived by such shadows in the pelvis, especially in patients with ascites and fluid within the pelvis. I do not know whether this is a cystic mass or whether it is fluid. Also on this film there are dilated loops of small bowel without evidence of marked distention and without a picture that suggests obstruction. About eight days later during this admission a cystogram was normal. Again, there is a density above the bladder shadow in the pelvis and more evidence of small-bowel distention, a few scattered loops of distended small bowel in the left upper quadrant, and a haziness over the abdomen that suggests ascites.

Dr. Chapman: This change in the heart shadow is actually striking.

Dr. Gibbons: Yes; it is. About three weeks after the second admission a bilateral pleural effusion had slowly developed. There is fluid in the left costophrenic sulcus and a small amount in the right side. The last film of the abdomen shows even more distention of small-bowel loops, with a configuration that suggests that they may be floating on fluid because they are gathered in the midportion of the abdomen. Their configuration also suggests that they may be fixed. This is not a reliable observation; it is just a possibility. On this particular film the shadow we saw in the pelvis on the other films is not so apparent although the débris in the rectum may hide that shadow. The liver is probably enlarged somewhat; thus, it is probably fluid within the pelvic peritoneum. The spleen does not appear to be enlarged.

Dr. Chapman: It was described as being enlarged to palpation.

Dr. Gibbons: In summary, the heart has a so-called mitral configuration with an enlarged left atrium. There are serial changes indicating pleural effusion, ascites, ileus and possibly a pelvic mass, the nature of which I do not know.

Dr. Chapman: The protocol said that the roentgenograms of the chest did not demonstrate any changes. It is quite revealing to me that there is some difference in the radiologist's findings and the report; this changes my opinion.

Although the evidence suggested renal failure at entry the patient recovered with what is called "elec-

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trolyte therapy." By the time of the operation the kidneys seemed to be removing waste products adequately, and the intravenous pyelogram was normal.

After a month in the hospital she may have had a pulmonary infarct, but this did not stay the surgeon's hand on the forty-sixth hospital day. Where was the incision made, and for what purpose? At this point I should like to say that I had been considering the popular operation called valvulotomy, but after looking at the changes in the x-ray films I wonder if nature had done a valvulotomy — if at some point along the line the mitral valve had ruptured? A rupture of the mitral valve would explain the obvious change in the configuration of the heart. At any rate the primary disease seems to have been the heart disease. Of course, to relieve chronic congestive heart failure, mitral valvulotomy has rarely been attempted in patients past the age of fifty. Recent experience, however, has shown that astonishing improvement has been accomplished by valvulotomy in a few persons over fifty. I doubt that this was done. Nor do I think that the evidence, other than that in the electrocardiogram, favors a chronic adherent pericardium that could have been released.

This leaves one other choice — to me the most likely: that the abdomen was opened and some type of tumor was removed. What was the nature of the tumor? I wondered if this mass might possibly have been encysted ascites; the patient had ascites and the x-ray films revealed the ascites, and yet the discrete mass suggests that possibly some of this fluid had been encapsulated. An ovarian cyst or fibroma could do this, and both have to be considered. I do not know how I can differentiate the two except that the mass was described as being very soft, which would favor the cystic tumor. The clinical history suggests that a tumor may have been twisting on its pedicle; then the torsion and infarction of the organ would have produced much of the pain and difficulty. In fact, at one time, I tried to explain the fall in blood pressure by the anoxia of a twisted pedicle of tumor; however, when I now see the changes in the outline of the heart, it seems to me that some intrinsic change in the heart rather than the acute episode within the abdomen explains the fall in pressure.

The Meigs syndrome — an ovarian fibroma, ascites and pleural effusion — has to be considered. The patient had pleural effusion; yet the tumor was very soft — it was hardly the solid tumor that one sees in this syndrome. Some obstruction within the portal veins has to be considered, but again there was insufficient clinical evidence. The pain when it started was in the upper abdomen, and later on it was across the back; the pancreas may have been the site of a vascular lesion that was sudden in onset, and, with that, pancreatitis may have occurred. We know that cystic tumors form in and about the pancreas after acute pancreatitis. Usually, the cystic tumors that follow pancreatitis present themselves higher in the abdomen; I have never heard of any as low as this tumor seems to have been outlined. I think that is about as far as I can go in considering the diagnostic possibilities.

In conclusion I think the patient had rheumatic heart disease. I was astonished to see the changes in the heart outline on x-ray examination and wonder now if something happened within the heart. Could she have had pericarditis with effusion at the time of the first admission that later led to the changes in outline and caused the electrocardiogram changes? I doubt it. I think she had had rheumatic heart disease, with mitral stenosis, and probably still had it, but obviously with fewer signs of it. The disappearance of the diastolic murmur does not bother me too much. We know that patients with chronic, prolonged rheumatic heart disease can have severe mitral stenosis when the examiners do not hear the diastolic murmur. In addition she was operated on for a tumor within the abdomen — what type I do not know.

DR. FRANCIS M. INGERSOLL: I should suggest that she had an ovarian neoplasm, a carcinoma, and that the ascites was on the basis of that.

DR. FARAHE MALOOF: Why do the films not show a mass impinging on the bladder?

DR. GIBBONS: If it were a cystic mass, it might not press upon the bladder; but it might not have been a mass, it might have been fluid.

DR. ROBERT H. FENNELL, JR.: Dr. Tuttle, would you tell us about the various opinions on the ward?

DR. ELBERT P. TUTTLE: On admission the patient presented the story of well controlled rheumatic heart disease, and I thought she had an abdominal emergency of some sort. My first impression was that she had had a renal stone; my second was that she had an intra-abdominal tumor, and I thought we could rule that out only by x-ray studies. Those studies were contradictory and confusing. There was the question of a pelvic mass that was seen in some positions and not in others. We were unable to withdraw fluid on paracentesis so that my final opinion when she went to the ward was that she was in low-grade chronic heart failure, with oliguria and unresponsiveness to mercurial diuretics. It seemed a matter of trying to pull her out of her heart trouble. Our studies had produced nothing definite, but she was obviously sicker than the degree of heart failure indicated.

DR. FENNELL: As I understand it, you were not at all sure that there was a mass and the laparotomy was done for a diagnosis.

DR. TUTTLE: That is correct.

CLINICAL DIAGNOSIS

?Abdominal cancer.

DR. EARLE M. CHAPMAN'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis.
Abdominal tumor, ?ovarian cyst.

Anatomical Diagnoses

Adenocarcinoma of right ovary, with metastases to peritoneum, pleura and pericardium.
Rheumatic heart disease, with mitral stenosis.

Pathological Discussion

Dr. Fennell: At the time of laparotomy it was found that the small bowel was matted together with a plastic exudate; this process, which was widespread, involving a great deal of the peritoneum, was thought to be a typical subsiding peritonitis. The puzzling part of it was that there was no obvious source — no appendicitis, no ruptured peptic ulcer or gall bladder and no perforation of the bowel. Cultures were taken, and the abdomen was closed. Biopsy of the omentum, however, was done, and the appendix was removed. It was not until we examined the biopsy of the omentum microscopically that we were given any clue to the actual process. The exudate was a carcinoma coating the omentum, and it was undifferentiated, with sheets of pleomorphic cells containing quite large nuclei and tending in some places to form acini. We were not sure where this came from but thought it might be from the ovary or possibly the breast. The patient deteriorated gradually and died approximately six weeks after the operation.

At autopsy there was some fluid in the peritoneal cavity and great masses of tumor, obvious at this time, matting together the loops of bowel and involving the mesentery. In the right lower quadrant there was a large mass of tumor into which the right tube extended; no right ovary was identified. The left ovary was normal in appearance. This tumor had extended upward, had implanted on the diaphragm and had extended through the diaphragm to involve the pericardium and left pleural cavity. There was a massive pleural effusion on the left. Histologically, the tumor was identical with that seen in the biopsy. In view of the histology, the behavior of the tumor and the replacement of the right ovary, it seems likely that the tumor was a carcinoma arising from the right ovary.

She also had severe mitral stenosis. The mitral-valve opening was buttonhole in shape, about 3 cm. long and a little more than 1 cm. wide. There was no evidence of active rheumatic fever, and none of the other valves were involved.

Dr. Maloof: Was a paracentesis ever done?

Dr. Tuttle: We attempted a paracentesis when she first came in because she seemed to have fluid in the abdominal cavity, but we were unable to draw anything back. Then she became so critically ill that we made no further attempt.

Dr. Allen G. Brailey: It seemed to me that the changes in the blood pressure were passed over very lightly; I think it is an amazing story.

Dr. Tuttle: We did not know what caused that. On the first admission the patient had a marked hypertension; over the course of the years that she was followed in the Out Patient Department it gradually subsided.

Dr. Maloof: Did she have an old infarct? The electrocardiogram suggests that she did.

Dr. Fennell: No; she did not. She had a slightly enlarged heart; the left ventricle was slightly thickened, but the coronary arteries were not diseased.

Dr. Chapman: The electrocardiogram done on the final admission shows changes that suggest infarction but are consistent with invasion of the pericardium.

CASE 40032

Presentation of Case

First admission. A seventy-two-year-old retired elevator operator was referred to the hospital because of an abnormal shadow on a chest roentgenogram.

One month before admission his chronic nonproductive cough had become more frequent and productive of whitish or yellowish phlegm, with occasional blood streaking. He had lost about 12 pounds during the month. Chest roentgenograms taken at another hospital demonstrated an area of homogeneous density extending from the hilus into the right lung, with obliteration of the cardiophrenic angle.

Physical examination showed a well developed and well nourished man. There was dullness, decreased breath sounds and decreased tactile fremitus at the right base. The heart was slightly enlarged, the border extending to the left, with no murmurs. The liver edge was palpable three fingerbreadths below the right costal margin. The prostate was one and a half times the normal size.

The temperature was 100.3°F., the pulse 112, and the respirations 22. The blood pressure was 140 systolic, 86 diastolic.

The urine was normal except for the sediment, which contained 2 to 10 white cells per high-power field. Examination of the blood disclosed a hemoglobin of 15.5 gm. per 100 cc. and a white-cell count of 11,900, with a normal differential. Serum chemical determinations were normal.

A roentgenogram of the chest revealed "atelectasis" in the posterior basilar segment of the right lower lobe. On bronchoscopy the "right middle lobe orifice was a little irregular and involved in a red, nodular process causing complete obstruction of the right-lower-lobe bronchus." A diagnosis of squamous-cell carcinoma was made from the biopsy, and a total pneumonectomy on the right was subsequently performed. Pathological examination of the specimen was reported as squamous-cell carcinoma, Grade 3, with metastases to the bronchial lymph nodes." The patient was ambulatory on the fifth postoperative day, but on the thirteenth day he began to cough up fluid that was similar to that

aspirated from the right side of the chest. Air-fluid levels to the fifth rib developed, but he continued to feel well and was discharged eighteen days after operation.

Second admission (nine days later). A trocar thoracotomy was performed, with insertion of drains into the right side of the chest. *Haemophilus influenzae* was cultured from the fluid, though he was afebrile at the time.

Third admission (four months later). There had been intermittent loss and replacement of the drain until a week before admission, when it came out and was not replaced. The temperature rose to 103°F., and he was readmitted to have a "large amount" of purulent fluid drained. He was discharged two days later.

Fourth admission (nine months later). The drain was omitted for eight months and the wound in the right side of the chest healed. Pain and tenderness in the lower right side of the chest again developed, and spontaneously the old wound broke down and drained pus. The drains were replaced. He was active, with minimal exertional dyspnea. X-ray films of the chest and physical examination demonstrated deviation of the trachea to the right, emphysema of the left lung and considerable air in the right half of the thorax.

Final admission (six and a half years after pneumonectomy). After discharge he was seen in the Out Patient Department because of urinary frequency and urgency. The prostate was smooth and enlarged to twice the normal size. There were episodes of recurrent, severe pain in the anterior part of the chest on exertion that were completely relieved by nitroglycerin. The electrocardiograms were normal. He slept on two pillows but had no nocturnal dyspnea and no ankle swelling. The catheter had been in place in the chest without causing pain or excessive drainage. He had taken sulfisoxazole, 4 gm. a day, since being seen in the Emergency Ward a week before admission with urinary complaints. He became weaker during the week before entry and frequently muttered unintelligibly, and urinary frequency, urgency and occasional incontinence continued. His cough was productive of a cupful of sputum a day. On the day of admission he walked to the bathroom and fell. When his daughter found him he was momentarily unable to speak and was cyanotic. En route, he had two more episodes of cyanosis within minutes of each other.

Physical examination revealed labored breathing with loud rattles, weakness with inability to cough well and slight cyanosis. The thoracotomy wound had a catheter in it and "sucked air with each respiration." The right side of the chest was dull; the left had loud bronchial rattles that obscured the heart sounds. The trachea was well over to the right. The neck veins on the right were distended to the jaw, and those on the left were flat. The liver edge was barely palpable. Neurologic examination was negative.

The temperature was 100.6°F., the pulse 118 and regular, and the respirations 40. The blood pressure was 110 systolic, 70 diastolic.

The urine was cloudy and gave a ++ test for albumin; the sediment contained 6 to 8 red blood cells per high-power field. The white-cell count was 25,300, with 82 per cent neutrophils. A stool guaiac test was negative. An electrocardiogram taken at the time of entry was not abnormal, with Q waves present in Lead 3 and upright T waves in Lead 3 and aVF.

Fifteen hundred cubic centimeters of urine was removed by catheterization. A sputum culture later grew out abundant pneumococci. An hour and a half later breathing suddenly became labored, with increased tracheal rattles and drop in blood pressure to 60 systolic, 50 diastolic. The patient died two hours later.

Differential Diagnosis

Dr. Helen S. Pittman*: I think the first four admissions, all of which took place within a year, are Volume I, which gives background material but can be put on the shelf and need not be consulted too much. During the second admission *H. influenzae* was cultured from the draining fluid; however, I suspect that the purulent fluid drained at the third admission contained mixed organisms. I assume that if cytologic studies had been done on that fluid, they would have been negative; otherwise, I should not be talking about the illness six and a half years after the removal of the squamous-cell carcinoma. This might be a good point at which to review the x-ray films and thus to dispose of the squamous-cell carcinoma with the positive lymph nodes.

Dr. John F. Gibbons: The set of films made during the first admission show a shadow in the lower medial portion of the right-lung field that on the lateral and oblique views is seen to occupy the posterior basilar segment of the right lower lobe; this presumably represents complete collapse of the lower lobe. The left lung looks normal, and the heart is normal except for slight prominence of the left ventricle. The next set of films, made about eighteen months later, demonstrate considerable contraction of the right pleural cavity, and the heart has shifted to the right side. The left lung has become emphysematous, and the right lung contains a pocket of air below which there is a density presumably made up of some thickened pleura and an indeterminate amount of fluid. The next films, made over two years after the original operation, show thickening of the pleura all the way up along the lateral chest wall, again a flat shadow at the right base and presumably some fluid remaining in the chest cavity on the right.

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DR. PITTMAN: That is also what I should assume. Can you say whether the right leaf of the diaphragm is elevated? I note that the liver edge was three fingerbreadths down at the first examination and later on apparently it was less easily palpable; I thought that was probably associated with the rise in the right leaf of the diaphragm.

DR. GIBBONS: I cannot see the diaphragm because of the thickened pleura and fluid, but I assume that it was considerably elevated; it always rises as the cavity contracts after a pneumonectomy.

DR. PITTMAN: The patient continued to have an open communication to the right pleural cavity and some difficulty with the prostate but was otherwise quite well for the next six and a half years.

On physical examination at the time of the final admission the thoracotomy wound "sucked air." That is not at all an uncommon phenomenon. If anyone is classically minded — the emphasis now is on a liberal education for physicians — in a paper on sucking wounds at the Battle of Stiklestad in Norway in 1015 Philip Giddings,* formerly on our Surgical Service, points out that sucking wounds were rare before the introduction of gunpowder. I think I shall dispose of the sucking wound with that classic reference.

In summary, there are, I think, three aspects of this problem: a six-and-a-half-year apparent cure of a squamous-cell carcinoma of the lung that at the time it was removed had involved the regional lymph nodes, with a subsequent pleurocutaneous fistula; increasing size of the prostate, with infection and increasing ureteral obstruction; and a one-week terminal illness. The terminal illness in an old man who was debilitated and had for a long while lived on borrowed time was characterized by weakness, productive cough, cyanosis, labored breathing with loud rattles, distended neck veins on the right, negative neurologic examination, fever, leukocytosis, falling blood pressure, infected urine, pneumococci in the sputum, urinary retention, hypotension and death two hours after catheterization with removal of 1500 cc. of urine. I should like to ask whether the nonprotein nitrogen level had been determined in recent years.

DR. EDGAR B. TAFT: It was 58 mg. per 100 cc. on the day before death.

DR. PITTMAN: Elevated, but not uremic, so that disposes of several of my diagnoses.

The distention of the neck veins on the right with normal veins on the left rules out anything in the pericardium because I believe lesions there could not involve the veins on one side of the neck and not the other. It seems to me that that finding reduces the possibilities to local obstruction of the veins by either thrombosis or tumor in or around the external neck veins. I assume that there was no edema of the right arm since it was not mentioned.

*Giddings, W. P. and Magoun, F. P., Jr. Sucking wounds at battle o Stiklestad. *Etudes germaniques* January–March, 1950. Pp. 31-34.

These findings could have been the result of any one of four conditions: a primary pneumococcal infection, with pneumonia and perhaps bacteremia; cerebral thrombosis with pulmonary congestion, although admittedly in the face of a negative neurologic examination; thrombosis or neoplastic obstruction of the veins of the right side of the neck and associated pulmonary congestion; and uremia, that is now proved not to have been present, with secondary bacterial infection and congestive heart failure. A great many arguments can be advanced for each little point in this record, but since I am unable to make a satisfactory diagnosis, a detailed discussion of those points would be nonproductive. Therefore, I shall say that there was no recurrence of the carcinoma and that the surgeon, who I suppose was Dr. Carroll C. Miller since he is here, had cured the patient. It seems to me that a patient who had positive lymph nodes six and a half years before admission would not have continued in fair health, but would have manifestations of recurrent disease long before this. He did not have uremia, but he certainly had outflow obstruction. He had pneumococci in the sputum and rattles in the chest. He may have had pneumococcal pneumonia or only congestive heart failure with the heart signs obscured by the rattles. He was old and debilitated and had had empyema for years; therefore I shall say that he had a pneumococcal bacteremia and failure of the left ventricle as well. I believe that thrombosis, not pressure from neoplastic tissue, caused the distention of the neck veins.

Now I come to the critical question, Does it do anybody harm to have his bladder drained all at once? Of course we are all taught that it does. If anyone can find references in the physiologic literature I should like to know about it. I have discussed this with three members of the urologic staff. One says that if somebody in whom a catheter cannot be placed comes in with urinary obstruction, the surgeons do a suprapubic cystotomy and drain the bladder completely — and nothing happens! I am told by another that decompression followed by shock has been reported by competent observers in the past, and there must be something in it. The patients who come into this hospital seldom have more than 800 cc. to 1000 cc. in the bladder, and perhaps the critical amount is over a liter, but the principle is to empty the bladder completely. Still another member of the department has emptied the bladder as rapidly as possible to see whether anything would happen, and it has not. Therefore, although the weight of authority is on the other side, I shall say that the catheterization of the poor decrepit old man was the last straw and that he died in shock, which it seemed to me it was, and in pulmonary edema two hours after the complete decompression of the bladder and that death was directly attributable to the removal of 1500 cc. of urine from the bladder.

DR. EDWARD B. BENEDICT: Do you think he may have had a cerebral metastasis that would account for all of it?

DR. PITTMAN: I think he may have had cerebral metastases or cerebral thromboses, but the neurologic examination was negative. I decided after weighing the various pros and cons that this man had every right to get sick and cyanotic, and took the position that he did not have any metastases.

DR. LEWIS W. KANE: Do you think this could be explained as the result of overwhelming infection from the pleural cavity?

DR. PITTMAN: The pleural cavity had been infected for six and a half years and there was *H. influenzae* in it the first time it was cultured. I think he may have had overwhelming infection, which is why I said he had bacteremia in the end; I assume that if it was pneumococcal it was probably a recent infection.

A PHYSICIAN: I once saw a patient whose bladder was rapidly drained and who went into shock and died within a matter of minutes.

DR. STUART RAGLAND, JR.: We have had several patients who have been either catheterized or cystoscoped and in whom a fulminating septicemia has developed very shortly thereafter. I cannot say that we have seen a death that occurred as dramatically as an hour and a half after the procedure, but 2 patients who had septicemia died within forty-eight hours.

DR. PITTMAN: Dr. Miller, did you cure this man the way I think you did?

DR. CARROLL C. MILLER: I think we probably did. Your argument based on the duration of life after the operation, I think, is sound; most of these patients with squamous-cell carcinoma, Grade 3, with positive lymph nodes, die within about two years.

DR. JACOB LERMAN: I was responsible for the patient on the last admission, but unfortunately he died before I saw him. On the data presented to me I too came to the conclusion that death was probably precipitated by rapid decompression of the bladder complicated by septicemia.

CLINICAL DIAGNOSES

Arteriosclerotic heart disease, with old myocardial infarction.
?*Escherichia coli* septicemia.
Acute and chronic pyelonephritis.
Pleurocutaneous fistula, post pneumonectomy.

DR. HELEN S. PITTMAN'S DIAGNOSES

Cancer of lung, cured by pneumonectomy.
Pneumococcal pneumonia and bacteremia.
Death in shock, with pulmonary edema, after catheterization.

ANATOMICAL DIAGNOSES

(*Squamous-cell carcinoma of right lung with regional-lymph-node metastases*) *six-year cure after pneumonectomy.*
Bronchopneumonia, left lower lobe, severe.
Pleurocutaneous fistula, post pneumonectomy.
Benign prostatic hypertrophy.
Acute and chronic pyelonephritis.
Congenital cortical cysts of kidneys.

PATHOLOGICAL DISCUSSION

DR. TAFT: Unfortunately, we as pathologists cannot prove or disprove the effect of catheterization. The prostate was quite enlarged, with a large median lobe that was pedunculated and extended into the bladder. The bladder was markedly hypertrophied and contained a few small stones. The kidneys were very large, weighing 800 gm., not because of hydronephrosis, but because they contained multiple cortical cysts, which were much more prominent in the left kidney. After the fluid had been removed from the cysts, the combined weight of the kidneys was 400 gm. which is not too abnormal.

Microscopical examination of the kidneys showed largely the changes of nephrosclerosis with a few small abscesses consistent with minimal acute pyelonephritis. The clinicians thought that this patient had a septicemia as Dr. Pittman did, but blood cultures at the time of autopsy revealed no growth despite the fact that it was planted on a number of mediums. The abscesses may be best explained on the basis of a bacteremia from the lesion of which the patient undoubtedly died — a severe confluent bronchopneumonia, which occupied the greater part of the left lower lobe. The lung was very much enlarged, weighing 860 gm.; the upper lobe, in addition to being emphysematous, was congested and edematous.

The patient was of considerable interest to us because, as Dr. Miller and Dr. Pittman have both suggested, there was no evidence of tumor at the time of autopsy. The right pleural cavity was largely obliterated except for a small pyramidal cavity toward the apex of the space that had a fistula between it and a small cutaneous opening at the right fifth rib in the anterior axillary line. The bronchial stump was healed, and there was no communication between the bronchus and the pleura.

DR. MILLER: How did you account for the neck-vein swelling?

DR. TAFT: There was no mention in the protocol of the examination of the veins in that area.

DR. MADELAINE R. BROWN: Was the brain examined?

DR. TAFT: Yes; and it was normal. The heart was normal too although the clinicians thought the patient had coronary-artery disease. The coronary arteries were widely patent and showed practically no atherosclerosis.

DR. PITTMAN: The cyanosis and failure were due to the pneumonia in most of the remaining left lung.

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"INTEGRATED" AND "COMPREHENSIVE" MEDICINE

GREAT progress has been made in medicine in various technical ways, but it appears at times that the human side of medicine — the relations between physician and patient, or the art of medicine — has been increasingly sacrificed, perhaps because of the dependence on laboratory medicine and the advance of scientific methods in general, the increase in specialization, the greater frequency of hospitalization and the decreasing care of the sick in the home. It is undoubtedly true that there has seemed to be less opportunity to observe and study other aspects of the patient than his presenting symptoms and his actual disease. Perhaps with an increase in pressure on the medical-school curriculum there has been little emphasis on teaching of this phase of medicine. It has been left to be acquired in actual practice.

The general practitioner knew the patient — his habits, his personality, his relation with the family and the community — and thus could offer help to the patient in other ways than medical despite the lack of the skilled diagnostic and technical methods of today. The "group clinic" of today can bring to the patient the diagnostic and therapeutic abilities of many specialties but often fails to supply the personal relation between the patient and physician. The introduction of social service in the hospitals by Dr. Richard C. Cabot years ago was an attempt to fill this gap.

In the past few years attempts have been made to remedy the situation further. "Integrated medicine"[1] has been a joint enterprise for the past seven years of the Department of Psychiatry of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School. The term means the treatment of the patient who is ill rather than exclusive attention to the diseases of organs and cells. It attempts to balance specialization by reviving the attitude of the family physician.

During the first two years lectures are given on normal emotional development, patient-physician relations and so forth, and patients are used to illustrate the influence of the family situation on disease in the patient. In the third and fourth years, in the actual care of patients, further emphasis is placed on physician-patient relations and the deeper emotional conflicts affecting disease, with a view to increasing the young physician's capacity for understanding and helping patients. It can therefore be considered also a study of the young physician and a realignment of his personality to make him a more successful practitioner.

In much the same vein in Philadelphia at the University of Pennsylvania the Department of Psychiatry has developed "comprehensive medicine." This term connotes a consideration of the patient as a person and teaches students to look beyond the disease to the patient and from the patient to the family, and behind the family to his cultural and religious background. Its purpose is expressed as "putting the family back in medical education."[2] In the Family Advisory Service at this

school the student is assigned a family, making the contact through a member who has been a patient in the hospital or outpatient department. He acts as friend and medical adviser of the family for his four years and visits the family once a month, or oftener if there is illness, injury or some emotional conflict. He can call on faculty advisers in emergencies, and he is expected to discuss his problems with other students and a faculty group that meets once a month for this purpose.

It is pointed out that over the years knowledge has proved that bacteria, toxins, trauma and tumors can change human chemistry and physiology, but at the same time it has been demonstrated that fear, anxiety, resentment, environmental conditions and family stresses are important factors in the patient's response to medical and surgical therapy. The treatment of the whole patient is an integral part of the practice and art of medicine. Thus "integrated" and "comprehensive" medicine are attempting to round out the teaching of medicine to provide a better basis for the more personal relation between patient and physician.

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INTIMATIONS OF IMMORTALITY

For one reason or another health, in all its ruddy aspects, continues to dog the footsteps of the generally well fed, well clothed and sanitarily regulated American public. Such, at least, are the conclusions to be drawn from the compilations of those avid delvers into the actuarial problems of the nation — the statisticians of the Metropolitan Life Insurance Company.

The health record in the United States was excellent in 1953 and bids fair to continue at its present high level. The death rate for the year recently ended was 9.6 per 1000 population, or about the same as the all-time record established in 1952; for six successive years the rate has been below 10. This record, moreover, was attained despite an epidemic of respiratory infections early in the year and the late summer heat wave, both of which took their toll of the aged and the chronically ill.

The mortality from tuberculosis has shown the greatest reduction, being less than 13 per 100,000 population in 1953; this rate, which is half that of 1949 and a third that of 1943, represents a decline of approximately 25 per cent since 1952.

The infant and maternal health record has continued to be favorable, and that for children unusually good; measles has been of low prevalence in addition to its partial control with gamma globulin, and whooping cough and diphtheria have continued to respond to the wide use of immunizing procedures. Mortality from scarlet fever has practically disappeared.

The incidence of poliomyelitis, although relatively high, declined nearly 40 per cent from its record year of 1952, also with a declining case fatality, the death rate for 1953 having been about 1 per 100,000 population. The death rate from acute respiratory disease showed a moderate increase over 1952, largely owing to influenza, although the rate from pneumonia, which is practically inseparable from the influenza rate, rose about 2 per cent.

As might be expected with a declining death rate from infectious diseases and those of infancy, that from chronic disease rose somewhat. After all — and perhaps fortunately — physical immortality is not yet in view, Wordsworth's intimations of it having presumably been spiritual in nature.

Despite the lurid headlines the death rate from homicide showed a decrease, possibly to its lowest level in twenty years, with the suicide rate definitely below the postwar average. The death rate from motor-vehicle accidents showed no appreciable change, despite the increase in the number of cars and in their mileage. At the time this report was issued, however, the carnage of the Christmas weekend had not been recorded, nor had that of New Year's Eve, when there is likely to be as much wringing of hands as of bells.

No separate figures were reported for deaths resulting from airplane accidents; these should also become part of the record.

On the whole, time and human progress seem to refute the lugubrious adage that only the good die

young. Under modern conditions of hygienic living the worthy seem to have as fair a chance of survival as the wicked.

TOBACCO AND CARCINOMA OF THE LUNG

PRESENT evidence of a correlation between smoking and cancer of the lung was further strengthened by a recent study, which reports a significant production of skin cancer in mice painted with a condensed cigarette tar.[1] Although previous studies had shown that occasional skin cancer is produced in mice and in rabbits with distilled tobacco-tar products, this represents the first record of a significant number of skin cancers caused by a cigarette tar produced under conditions simulating human smoking habits.

It may be asked what significance, if any, such a finding has on the problem of cancer of the lung in human beings. Does mouse skin behave like human bronchial epithelium? Historically, there has been a close association between epidermoid carcinogenesis in mice and men. Studies with coal tar and various petroleum products serve as a good example. When this particular question is considered, however, it must be stressed that the animal experiments were undertaken because of the human evidence already at hand.

Today, thirteen separate studies from six different countries, involving more than 5000 patients, all point to a correlation between smoking and cancer of the lung. More than a year ago, in a symposium on lung cancer sponsored by WHO and UNESCO, such an association was regarded as established.[2] The statistical association is considered to have etiologic significance because it is compatible with the present sex ratio and incidence pattern of pulmonary cancer[3] and the urban-rural distribution, as well as the fact that this association could not be readily explained upon any other basis. The association between smoking and cancer of the lung does not deny the significance of other factors. Individual predisposition is of undoubted importance although its nature is not understood. Some occupational exposures seem to lead to higher than expected risk. Air pollution has been mentioned as an added factor, although statistical clinical proof is lacking. As a matter of fact, Doll[4] recently pointed out that a nonsmoker in a city has as little chance of acquiring cancer of the lung as a nonsmoker living in a farm area.

Even though the role of other etiologic factors is recognized the fact remains that statistical clinical data show that nonsmokers rarely have lung cancer, whereas the risk increases directly with the amount of tobacco smoked. It is because of the extensive human evidence that the new experimental data gain significance.

According to the authors of this investigation the primary purpose of experimental tobacco-tar studies is not so much to confirm or deny human data, which they believe must stand essentially on their own merits, as to serve as a research tool for the possible identification of actual carcinogens in tobacco tar. At present it can only be speculated that these agents will be the same as those affecting man. Such work of identification could only be done with the laboratory animal.

Thus, because of the massive clinical statistical evidence collating smoking to cancer of the lung and because of the ever-increasing incidence, further experimental work that may lead to the identification and possible removal of carcinogenic agents from tobacco tars appears most urgent. It might be timely for the manufacturers of cigarettes, some of whom have adopted the policy of discrediting this obvious association, to take an even more active interest in the detection and elimination of the carcinogenic factors.

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MISSING LINK

IN 1911 an amateur anthropologist unearthed from a gravel pit in the Sussex downs the osseous remnants of what has been considered an important link in the long chain of developmental events connecting man with his primordial ancestors. The

"Piltdown man," consisting of a cranium, a jawbone of uncertain status and a tooth — something more and something less than Kipling's "rag and a bone and a hank of hair," representing all womankind — has constituted to some scientists the true missing link.

Not all anthropologic savants, however, have been willing for these forty-two years to accept the Piltdown man as a genuine relic, despite the monument erected to his resurrectionist on the spot where he was found. And now the Piltdown man, as of last November, has been thoroughly discredited by chemical tests proving that the jawbone is not that of a man of any sort, but of a modern ten-year-old ape, resculptured by the hand of modern man and artificially treated to give it the appearance of a fossil.

Again monkeys have been made of men, this time by making a man of a monkey.

A note from the Superintendent of the Insane Hospital at Concord, N. H., says that the spermatorrhoea rings are very successful there.

Boston M. & S. J. *January 25, 1854*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 3, at 10:30 a.m. This meeting will be followed by the Cotting Luncheon.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held October 7, 1953, as published in Supplement No. 2, November 12, 1953.
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary

DEATHS

BOUVIER — John Joseph Bouvier, M.D., of Whitinsville, died on November 13. He was in his forty-eighth year.

Dr. Bouvier received his degree from Georgetown University School of Medicine in 1932. He was civil-defense area medical director, a member of the staff of the Whitinsville Hospital, the American Academy of General Practice and the Massachusetts Heart Association, and a fellow of the American Medical Association.

He is survived by his widow, two sons, his mother, a brother, two sisters and several nieces and nephews.

COOPER — Edward Cooper, M.D., of Worcester, died on November 5. He was in his eighty-fifth year.

Dr. Cooper received his degree from Jefferson Medical College of Philadelphia in 1905. He was a fellow of the American Medical Association.

He is survived by his widow, a daughter, three grandchildren and several nieces and nephews.

KICKHAM — Charles J. Kickham, M.D., of Brookline, died on January 4. He was in his sixty-ninth year.

Dr. Kickham received his degree from Tufts College Medical School in 1908. He was chief of gynecology, St. Elizabeth's Hospital, a fellow of the American College of Surgeons and the American Medical Association, and a member of the New England Obstetrical and Gynecological Society. He was a councilor of the Massachusetts Medical Society and was formerly president of the Norfolk District Medical Society, vice-president of the Massachusetts Medical Society and a delegate to the American Medical Association.

He is survived by his widow, three sons, a daughter, a sister and two grandchildren.

STANTON — Joseph Stanton, M.D., of Boston, died on January 2. He was in his seventy-sixth year.

Dr. Stanton received his degree from Harvard Medical School in 1903. He was formerly chief of staff, St. Elizabeth's Hospital, Brighton, and a member of the staff of the Newton-Wellesley Hospital. He was a fellow of the American College of Surgeons and the American Medical Association.

He is survived by his widow, five sons and five daughters.

BOSTON MEDICAL LIBRARY

TUFTS MEDICAL ALUMNI BULLETIN

The issue of the *Tufts Medical Alumni Bulletin* for November, 1953, is unusual, containing a picture and a brief account of the new president of Tufts College, Dr. Nils Y. Wessell, and biographical sketches of the late Drs. Louis E. Phaneuf and Frank H. Lahey, formerly members of the medical faculty and prominent Boston specialists. There are also articles on the Department of Ophthalmology by Dr. Benjamin Sachs, on Dr. Roy J. Heffernan, new chief of gynecology and obstetrics at the Carney Hospital, and on Dr. Patrick J. Fitzgerald (Tufts College Medical School, 1940), the new professor of pathology at State University of New York College of Medicine. There is also a short account of the Boston Medical Library and its functions, and the usual alumni notes.

CORRESPONDENCE

MAINE MARITIME ACADEMY CRUISE

To the Editor: I am writing again to request your assistance in obtaining a doctor to accompany us on our winter cruise. In past years your publication has been instrumental in obtaining the services of a doctor.

The cruise will be two months in duration, departing January 29, and will make ports of call in Puerto Rico, Haiti, South America, Jamaica and Cuba.

Our training ship is provided by the United States Maritime Administration and is a 400-foot steamer equipped as a training vessel. Embarked will be the cadets, faculty and staff of the Academy, amounting to 260 persons. It has been our custom in the past to employ a doctor for this cruise, which is tantamount to a vacation with pay for him owing to the fact that all persons on board are in excellent physical condition. However, we desire a doctor on board in case of emergencies. Anyone interested should communicate with the undersigned at the Academy (telephone, Castine 69).

W. W. Warlick
Rear Admiral, USN (Ret.)
Superintendent

Maine Maritime Academy
Castine, Maine

MASSACHUSETTS HEART ASSOCIATION

To the Editor: The purpose of this letter is to invite all members of the Massachusetts Medical Society to membership in the Massachusetts Heart Association.

Seldom, it is believed, have so many privileges and benefits been offered for so little money. The dues are $3 a year; benefits include membership in the New England Cardiovascular Society, a bound copy of the annual *Proceedings* of the Society, notices of all meetings of the Society, twelve monthly issues of *Modern Concepts of Cardiovascular Disease*, occasional other professional publications, helpful publications for patients, on a prescription basis such as *Cook Book for Low Sodium Diet* and voting privileges in the American Heart Association and the Massachusetts Heart Association.

The membership year started on January 1, 1954. Requests for membership should be addressed to Membership Secretary, Massachusetts Heart Association, 650 Beacon Street, Boston 15, Massachusetts.

Lewis M. Hurxthal, M.D.
President
Massachusetts Heart Association

Boston

SOLOMON CARTER FULLER — 1872–1953

To the Editor: The following tribute to Dr. Solomon Carter Fuller was read by Dr. James B. Ayer before the Boston Society of Psychiatry and Neurology on November 30.

Wilfred Bloomberg, M.D.
Secretary

Boston

Dr. Fuller's life story is well worth summarizing, for it represents the progressive rise of a man, handicapped by alien birth, by poverty and absence of friends, to a position of trust and competence:— a story which we like to believe can only happen in America.

He was born in Monrovia, Liberia, August 11, 1872. Spurred on by a desire for a better education, he came to the United States at seventeen to attend Livingstone College at Salisbury, North Carolina, receiving his A.B. in 1893. His mental urge now was for medicine and, for some unknown reason, he came to Boston with little money in his pockets and little knowledge of where to go. His widow relates that he wandered about Boston, and finally came to Boston University. He must have had a wistful expression for, as he looked, the dean came down the steps and asked him if he had come to register in medicine, later offering a scholarship which he declined. The dean must have been very observing to so quickly recognize a foreigner who would graduate M.D. in 1897 and later fill the post of professor of neurology for twenty-three years (1909–1932).

His position at the Westboro State Hospital in pathology and clinical psychiatry in his early medical career (1897–1920) was his introduction to the neurological and psychiatric field. Best known was his work on the dementias, and several papers on Alzheimer's disease, in which he employed the newly discovered silver stains. In 1911, he published the ninth case of this disease. It is interesting that, in a paper of 1912, his critical judgment questioned the significance of plaques and neurofibrillar changes as pathognomonic of Alzheimer's disease, and ventured the hypothesis that something other than arteriosclerosis must be the cause, a point of view upheld by Neumann and Cohn in 1953.

He must have been an assiduous worker for he made his own photomicrographs after hours. Moreover, for many years, he maintained an office in his home in Framingham, as also in Boston, yet he led a versatile life and he and his wife had mutual hobbies such as gardening and bookbinding.

In 1943, he returned to Livingstone for his fiftieth reunion, and there received the coveted D.Sc. for outstanding work in psychiatry.

Solomon Fuller died last winter in his eighty-second year. Shortly before, I saw and talked with him: though blind, his memory was excellent, his speech flawless, his interests alive. He knew he had not long to live, but accepted the fact in his usual, philosophical manner, like the perfect gentleman he was.

NATIONAL MUSCULAR DYSTROPHY RESEARCH FOUNDATION

To the Editor: Acting on the recommendation by the National Muscular Dystrophy Research Foundation's Research Advisory Board, of which Dr. D. Denny-Brown is chairman, the Board of Directors has currently made a grant of $5000 to Southwest Foundation for Research and Education in San Antonio, Texas. Entitled, "Individual Metabolic Patterns for Families Having a History of Muscular Dystrophy," the project is being conducted under the supervision of biochemist Dr. Roy B. Mefferd.

Foundation headquarters are co-operating in the selection of families who are subjects of the studies. Progressive changes in the metabolism of each subject will be compared both within and between families for a three-year period.

Those wishing to make application for moderate grants-in-aid should do so to the Executive Secretaries, National Muscular Dystrophy Research Foundation, Incorporated, 709 Main Street, Liberty, Texas.

A. L. Delaney, M.D.
President
National Muscular Dystrophy Research Foundation
Liberty, Texas

TWO FANCONI SYNDROMES

To the Editor: In view of the difficulty so frequently experienced in learning the proper combination of disorders when a man's name has been attached to a syndrome, attention is hereby called to the two Fanconi syndromes.

Hematologists and others familiar with hematologic writings of the past few years are acquainted with the term, "Fanconi's syndrome." It signifies for them a young patient with a congenital hypoplastic anemia, hypoplasia of gonadal tissues, frequently other developmental defects and, later, skin pigmentation due to hemosiderosis.

Those interested in metabolic disorders, in diseases of bone or diseases of the kidneys picture Fanconi's syndrome as a form of osteomalacia, with excessive renal loss of amino acids, glucose, bicarbonate, phosphorus, potassium and peptides. Acidosis eventually results in renal calculi, with changes in the tubules and glomeruli, cirrhosis of the liver or both. Others, who must be content to fall steadily farther behind the avalanche of medical literature while trying to cover a few journals in the broader field of medicine, find new diseases difficult to comprehend, this difficulty being greatly increased when one name is given to two completely different conditions.

A glance at any current medical dictionary will re-emphasize the vast number of syndromes that are virtually lost to medicine. A few from this list are used frequently and are familiar to all the medical profession. These argue heavily the convenience of using one man's name to signify a disease instead of naming it in terms of its many physiologic and anatomic derangements. Certainly, each of these two disorders described by Fanconi comprises a sufficient number of components to warrant the use of a brief name.

It seems worth while to call attention to this terminologic confusion and to propose general acceptance of the term used by Brick, deToni–Fanconi syndrome, for the metabolic disorder and Fanconi's anemia for the disease that has more recently received the attention of Estren et al. and Rohr.

EDWARD H. MCGEHEE, M.D.

Philadelphia

BOOK REVIEWS

Clinical Cardiology. Edited by Franklin C. Massey, M.D. 8°, cloth, 1100 pp., with illustrations. Baltimore: Williams and Wilkins, 1953. $13.50.

This publication presents the contributions of 33 authors, of whom 13 are on the faculty of the Hahnemann Medical College of Philadelphia, 3 others from the Philadelphia area, 5 more from the East Coast, 7 from the West Coast, 3 from the Midwest, 1 from the South, and 1 from the Army. In spite of these diversified backgrounds the editor has succeeded in collecting a group of papers in support of his three objectives — namely, to relate cardiology to other aspects of medicine, to present in easily available form the more recent advances in this special field and to supply a forum for controversial subjects; as a means of attaining the last objective some of the less widely accepted theories are presented.

The coverage is comprehensive, from the anatomy of the heart to the psychiatric implications of cardiology, although some of the chapters are reprints from earlier publications. The book is not overweighted with bibliography, but pertinent references are given. As an example of this, Lepeschkin's chapter on electrocardiography has 271 pages with one reference, — to his own volume on *Modern Electrocardiography*, but it should be noted that this volume contains almost 10,000 references to publications on the subject.

It is difficult to select individual chapters for special criticism. That on "The Normal Heart" by Likoff and Davie provides a good reference source of data sometimes hard to find in a single collection. As might have been expected from the activity in cardiovascular surgery in Philadelphia, this subject is well covered by Bailey, Glover, O'Neill and Wells.

Arteriosclerosis is thoroughly discussed by Hueper but is naturally described in terms of his special interest in the subject some years ago. One misses a consideration of some of the more recent work in the cholesterol and lipoprotein field, and of the influence of sex hormones in altering lipoprotein patterns. The relation of coronary arteriosclerosis to sex is covered in three sentences, one of which is that it has been noted "that coronary deaths occur less frequently among the population residing along the seashore of Sweden than among the urban population of Stockholm."

Cardiac arrhythmias are excellently described by Dr. DiPalma, and their therapy outlined in a logical, as well as a pharmacologic, manner.

The therapy of congestive failure is considered by Dr. Schemm, with emphasis on the influence of water as a diuretic.

Dr. Bonica's discussion of "Anesthesia and Surgery in the Cardiac Patient" is detailed and very good.

Dr. Massey, himself, has contributed to the valuable chapters on "Disturbances of the Coronary Circulation," "Myocarditis" "Pericarditis" and "Tumors of the Heart and Pericardium."

The book, which can be recommended for the reference shelf of any physician, including the cardiologist, has the virtue of eminent readability.

HOWARD B. SPRAGUE, M.D.

Direct Analysis: Selected papers. By John N. Rosen, M.D. 8°, cloth, 184 pp., with 1 table. New York: Grune and Stratton, 1953. $3.75.

"Psychotics do not differ in kind, but only in degree" — this statement is typical of the many conclusions drawn in this book, which is actually a compendium of nine papers and lectures delivered by the author at various meetings and published in psychiatric bulletins between 1946 and 1952. Dr. Paul Federn, in discussing one of Dr. Rosen's papers in 1946 suggested the term "direct analysis" for this new type of therapy. The author for terminologic convenience uses this phrase when referring to work with psychotic patients and "analysis" without qualification when referring to psychoanalysis of neurotic patients.

In theoretic formulations, direct analysis is an extension of Freudian theory with certain radical innovations and departures from ordinary psychoanalytic procedures where necessity demands. The dynamics on which the technic is based comes from dream psychology as defined by Freud. At times interesting if dogmatic statements are made, such as the following:

> Mental illness is a process in which various unworkable defenses are abandoned in the desperate retreat from reality. The individual is first neurotic, then at a deeper level obsessive-compulsive, then manic-depressive, then paranoid, and only after these stages does deep psychosis develop.

The road back from psychosis appears to be the reverse of the road down — advancing back from unreality the patient works his way stage by stage to a neurosis resembling that which he had before but attenuated by the whole experience of the psychosis and of the direct analytic treatment.

The papers, emphasizing ideas, technics and case materials, may leave the reader with the impression that this is all the therapy needed to cure psychoses. But years of experience have proved that direct analysis must be followed by routine psychoanalysis when the patient has recovered from his psychosis to restore him to full and permanent good health; because he has experienced so much of the unconscious and has acquired such sharp insights from the direct analysis, the mandatory follow-up analysis is easier.

The premise of direct analysis is that except when physical pathology can be clearly demonstrated, psychoses are psychogenic and are treatable by psychologic means. The author regards neurosis and psychosis as different only in degree or stage of illness: one is simply deeper than the other. So far as all men have an unconscious, they are all potentially psychotic. The concept of a neurosis is presented as an oedipal and that of a psychosis as an oral problem to be interpreted as such by direct analysis.

Dr. Rosen places great emphasis on genital, oral and anal interpretations, giving repeated examples of each and stressing the results obtained with oral interpretations in the psychosis, but paradoxically appears to make many genital interpretations.

Most of his work is with schizophrenic patients, invariably reared by a woman who suffers from a perversion of the maternal instinct, according to the author's hypothesis.

Every psychotic person passes through a phase in which a preponderance of paranoid symptoms exist. These, as well as the underlying psychosis, are caused by the mother's inability to love her child, and the child (regressed patient) expresses this faulty relation by his paranoid phase — he may hear voices that say, "You are rotten, you are no good, I hate you." This is a reflection of the rejecting mother's attitude of "Be still, be quiet, be dead."

The survival function of schizophrenic patients is briefly described. The development of a psychosis is necessary for the continuation of life. The patient develops a wish for something so important that it involves a matter of life and death — usually, it is unobtainable; the unconscious part of the psychic apparatus springs into action and by imagination provides the necessary gratification of the wish. That imagination comprises the delusions and hallucinations that constitute the psychosis.

Dr. Rosen's theories are substantiated by many case histories and verbatim accounts of the interview situation, usually indicating slow but progressive improvement. He is willing, at times, to admit failure or at least poor results and emphasizes the fact that he must frequently make ten interpretations before finding the correct one and that many of his failures are due to faulty interpretations.

ELOISE B. PETERSON, M.D.

This Is Your World: A book for the orientation of professional workers to the emotional problems of the chronically ill patient; tuberculosis and the individual. Written and illustrated by Harry A. Wilmer, M.D., Ph.D. in Path. With a foreword by Adelaide McF. Johnson, M.D., Ph.D. 8°, cloth, 165 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.50. (Publication No. 140, *American Lecture Series.*)

This is a unique book about an old and well known subject — namely, features of tuberculosis that are not strictly speaking "organic." For any physician who is interested in the personality of his patient, as well as his organs, the volume will prove invaluable.

Dr. Wilmer has gathered together all sorts of information, grouped in such a way that the result is readable and informative. The book utilizes charts, diagrams, pictures, illustrations, poems and prose fragments in an extremely human and readable way.

It could even be used by literate patients to increase their insight, if the doctor chose to recommend it. I, for one, definitely would, for I think the whole tone of the book is constructive and inspirational — a good job, well done, in an interesting way.

MERRILL MOORE, M.D.

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Basic Problems in Psychiatry. Edited by Joseph Wortis, M.D., Jewish Hospital of Brooklyn. 8°, cloth, 186 pp. New York: Grune and Stratton, 1953. $4.50.

This small volume presents 7 papers on the scope and limitations, and the physiologic basis of psychiatry, psychology and culture, the validity of mental testing, schools of psychiatry and the psychosomatic symptom. There is a long introduction of a general character and a final chapter on comments and conclusions by the editor. There is a good index, and the publishing is excellent. The book should be in collections on psychiatry.

NONCLINICAL NOTES

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The Association for Research in Nervous and Mental Disease announces the election of officers for 1954 as follows: president, Dr. Rustin McIntosh; first vice-president, Dr. Walter Klingman; second vice-president, Dr. William S. Langford; secretary-treasurer, Dr. Clarence C. Hare; assistant secretary, Dr. Rollo J. Masselink.

MASSACHUSETTS MEDICAL BENEVOLENT SOCIETY

The ninety-seventh annual meeting of the Massachusetts Medical Benevolent Society was held at 22 Fenway, on December 16, 1953. The treasurer, Dr. C. C. Lund, reported on grants made to twenty-two beneficiaries, the largest number ever to be dispensed by the Society.

Appropriate ways to increase the membership and activity of the Society, which has served a useful purpose in the Commonwealth for nearly a century, were discussed. Most of the members have joined for life by paying the annual dues of $5 for twenty years, but there are only 30 active participants at present. (Membership should include many of the younger members of the Massachusetts Medical Society, and during the coming year they will be urged to join.)

Three new council members were elected, as well as the following officers: president, Dr. Paul D. White; vice-president, Dr. Leland S. McKittrick; secretary, Dr. A. W. Reggio; and treasurer, Dr. C. C. Lund.

NOTICES

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Massachusetts Memorial and Beth Israel hospitals in Morse Auditorium, Museum of Science, Boston, February 8, at 8 p.m.

PROGRAM

Massachusetts Memorial Hospitals (Dr. Robert W. Wilkins presiding):

Observations on Insulin Induced Hypoglycemia in Patients with Angina Pectoris. Drs. Walter E. Judson and William Hollander.

Cardiovascular and Respiratory Responses to Hypertonic Saline Infusions in Patients with and without Congestive Heart Failure. Drs. William Hollander, Walter E. Judson and Richard W. Stone.

The Effects of Acute Salt Loads on the Urinary Excretion of Sodium in Hypertensive and Normotensive Patients. Drs. Jesse E. Thompson and Thomas Silva.

Beth Israel Hospital (Dr. Herrman L. Blumgart presiding):

Arterial Oligemia of the Lungs in Severe Mitral Stenosis. Drs. Felix G. Fleischner and Elliot Sagall.

An Improved Method for the Intravenous Administration of Heparin. Drs. Stanford Wessler and Jerome W. Fischbein.

Sublingual Erythrol Tetranitrate in Angina Pectoris. Drs. J. E. F. Riseman, George E. Altman, Lester A. Steinberg and Elliot Sagall.

Further Observations on Treatment of Stokes–Adams Disease with External Electric Stimulation of the Heart. Drs. Paul M. Zoll, Arthur J. Linenthal and Leona R. Norman.

All interested persons are invited.

NEW ENGLAND DIABETES ASSOCIATION

A meeting of the New England Diabetes Association will be held at Hanover, New Hampshire, February 26 and 27. Dr. I. M. Rabinowitch, of Montreal, will speak on the topic "Diabetes" at the Friday evening lectures, beginning at 8 p.m. A clinical conference will be held at the Veterans Administration Hospital, White River Junction, Vermont, on February 27, at 9:30 a.m. All interested persons are invited.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the New Lecture Room, Harvard School of Dental Medicine, 188 Longwood Avenue, Boston, on Tuesday, February 9, at 8 p.m. The program, which will be presented by the Harvard School of Dental Medicine (Roy O. Greep presiding), is as follows:

Recent Advances in Experimental Caries Research. Reidar F. Sognnaes, James H. Shaw and Paul H. Keyes.

Radioisotope Studies of the Oral Calcified Tissues. James H. Shaw, Reidar F. Sognnaes and Rita Bogoroch.

The Chemical Nature of the Organic Matrix of Dentine, Enamel and Bone. Maurice V. Stack.

Metabolic Studies of Mucous Membranes. David Weisberger.

Recent Studies on the Nature and Mechanism of Action of Parathyroid Hormonal Activity. Paul L. Munson, Alexander D. Kenny, Oscar A. Iseri, Bernard G. Vine and Svein U. Toverud.

Studies on the Adrenal Cortex of the Rhesus Monkey. Ernest Knobil and Roy O. Greep.

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

The eleventh meeting of the New York Society for Circulatory Diseases, affiliated with the American College of Cardiology, will be held in Room 440, New York Academy of Medicine, on Tuesday, February 9, at 8:30 p.m. The subject will be the new antihypertensive drugs. The speakers will be Drs. Rudolph E. Fremont and Milton Mendlowitz. Dr. Simon Dack will preside.

AMERICAN ACADEMY OF GENERAL PRACTICE

The sixth annual Scientific Assembly of the American Academy of General Practice will be held in Public Auditorium, Cleveland, March 22 through 25. Among the speakers will be Sir Alexander Fleming and Drs. Howard Rusk and E. J. McCormick.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The case abstracts for Part I of the American Board of Obstetrics and Gynecology are now due. Part II of the examinations will be held at the Edgewater Beach Hotel, Chicago, May 10 through 17. Candidates for re-examination in Part II must make written application to the secretary's office before April 1.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The thirty-first annual meeting of the American Orthopsychiatric Association will be held at the Hotel Commodore, New York City, March 11 through 13. There will be a session on residential treatment centers for emotionally disturbed children, films on mental health and a panel entitled "Causes of Family Breakdown." Further information may be obtained from Dr. Marion F. Langer, American Orthopsychiatric Association, 1790 Broadway, New York 19, New York.

INTERNATIONAL ACADEMY OF PROCTOLOGY

The sixth annual convention of the International Academy of Proctology will be held at the Palmer House, Chicago, April 8 through 11. There will be a motion-picture seminar on proctologic surgery. There is no fee for attendance, and all physicians are invited.

MID-WINTER RADIOLOGICAL CONFERENCE

The sixth annual Mid-Winter Radiological Conference, sponsored by the Los Angeles Radiological Society, will be held at the Ambassador Hotel, Los Angeles, February 20 and 21. Among the speakers will be Drs. Eugene P. Pendergrass, of Philadelphia, U. V. Portman, Tucson, Marcy L. Sussman, Phoenix, and Frederic E. Templeton, Seattle. Reservations may be made through Dr. Harold P. Tompkins, 658 South Westlake Avenue, Los Angeles, 57, California.

THE FOUNDATION OF THE AMERICAN SOCIETY OF PLASTIC AND RECONSTRUCTIVE SURGERY

The Foundation of the American Society of Plastic and Reconstructive Surgery offers two main prizes, each a scholarship in plastic surgery for three months, with full maintenance, in the United States and abroad. This contest is restricted to residents in training and to plastic surgeons who have been in practice less than five years. A thesis of 5000 words, in English, on original research (clinical or experimental), not previously published, on plastic and reconstructive surgery, must be submitted before July 1.

A silver plaque or a certificate of honorable mention will be awarded to the contestant in practice more than five years who submits the best essay. Further information may be obtained from the Award Committee, c/o Jacques W. Maliniac, M.D., 30 Central Park South, New York, New York.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 26. Massachusetts Hospital Association. Page 1130, issue of December 31.

JANUARY 27. Middlesex South District Medical Society. Page 38, issue of January 7.

JANUARY 29 and 30. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JANUARY 29–MAY 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.

FEBRUARY 1 and 15, MARCH 1 and 15, APRIL 5 and 19. Hartford Medical Society. Page 1130, issue of December 31.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 5. New England Society of Anesthesiologists. Page 87, issue of January 14.

FEBRUARY 8. New England Cardiovascular Society. Page 129.

FEBRUARY 9. New York Society for Circulatory Diseases. Page 129.

FEBRUARY 9. Harvard Medical Society. Page 129.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

FEBRUARY 20 and 21. Mid-Winter Radiological Conference. Notice above.

FEBRUARY 23–25. College of Medical Evangelists Alumni Postgraduate Convention. Page 1044, issue of December 17.

FEBRUARY 26 and 27. New England Diabetes Association. Page 129.

MARCH 3 and APRIL 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

MARCH 11–13. American Orthopsychiatric Association. Page 129.

MARCH 15–26. Course in Laboratory Diagnosis of Virus Diseases. Page 1044, issue of December 17.

MARCH 22–25. American Academy of General Practice. Page 129.

MARCH 27 and 28. American Psychosomatic Society. Page 1044, issue of December 17.

APRIL 8–11. International Academy of Proctology. Notice above.

MAY 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.

MAY 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

MAY 12. 113th Annual Meeting. Andover Country Club, Andover.

MIDDLESEX EAST

MARCH 24.

MAY 11. Annual Meeting. (Harlow Dinner.)

MIDDLESEX SOUTH

JANUARY 27. Jenkins Auditorium, Malden High School, Salem Street, Malden. 8:00 p.m.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 28

THURSDAY, JANUARY 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Pathology of the Thymus Gland. Dr. Benjamin Castleman. Stearns Auditorium, New England Center Hospital.

*4:00–5:00 p.m. Metabolic Requirements of Nutrition in Normal and Abnormal States. Dr. H. Minkel. Nurses' Home, Cambridge City Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JANUARY 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*12:30–1:30 p.m. Anorectal Disease. Dr. G. Angelo. Ward B Classroom, Cambridge City Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Boston Lying-in Hospital Journal Club. The X-ray Diagnosis of the Acute Abdomen. Dr. Richard Schatzki. Auditorium, Boston Lying-in Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JANUARY 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*9:00–10:00 a.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*10:30–11:00 a.m. The Treatment of Cardiac Arrest. Drs. Benjamin E. Etsten and Harry H. Miller.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

MONDAY, FEBRUARY 1

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main amphitheater, Peter Bent Brigham Hospital.

7:00–9:00 p.m. Combined Anesthesia Resident Training Program. Jimmy Fund Auditorium, Children's Medical Center.

(Notices concluded on page xxi)